FDA FOREIGN DRUG INSPECTION PROGRAM: A SYSTEM AT RISK

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

NOVEMBER 1, 2007

Serial No. 110–74

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FDA FOREIGN DRUG INSPECTION PROGRAM: A SYSTEM AT RISK

THURSDAY, NOVEMBER 1, 2007

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2123 of the Rayburn House Office Building, Hon. Bart Stupak [chairman of the subcommittee] presiding.

Members present: Representatives DeGette, Inslee, Dingell, Whitfield, Walden, Ferguson, Murphy, Burgess, and Blackburn.

Staff present: John Sopko, Chris Knauer, Scott Schloegel, Paul Jung, Joanne Royce, Kyle Chapman, Peter Spencer, and Alan Slobodin.

OPENING STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. STUPAK. This meeting will come to order. Today we have a hearing on the "FDA Food and Drug Inspection Program, a System at Risk." Each member will be recognized for 5 minutes for an opening statement. I will begin.

This hearing is a continuation of this subcommittee's investigations into the safety of imported products. Today we explore the question of whether the FDA is adequately regulating the manufacturing of pharmaceutical products and active pharmaceutical ingredients, or APIs, as they are called, for export into the United States. Most Americans do not realize that many of the drug products in their medicine cabinets come from overseas. In fact, more than 80 percent of the active pharmaceutical ingredients that go into drugs come from abroad. India and China account for almost half of these imports. India's pharmaceutical imports into this country have increased 2,400 percent from 1996 to 2006, making it the fastest-growing drug importer, and China has doubled its pharmaceutical imports to the United States over the last 5 years.

The Food and Drug Administration is responsible for regulating foreign-made medicines and ensuring the American public is supplied with safe medications. Despite a 2000 oversight hearing and a critical GAO audit in 1998, which pointed out many of the FDA's weaknesses regarding importation of drugs, the FDA continues to use 20th-century tools and resources to address 21st-century regulatory challenges.

Today's hearing is intended to determine the effectiveness of FDA in overseeing foreign drug production and explore what re-

sources the agency realistically needs to do the job. Unlike food products, FDA cannot rely on any testing to determine if the drug products are safe. Instead, FDA's main tool for ensuring that a drug is manufactured safely is to conduct actual onsite inspections of drug-making facilities. The FDA is required to conduct a formal, pre-approval inspection before a form, domestic or foreign, can begin producing drugs for the U.S. market. After a pre-approval inspection, the agency is required to conduct follow-up surveillance inspections of domestic facilities to ensure they are continuing to meet U.S. manufacturing regulations. For U.S. drug manufacturers, Federal Law requires that follow-up inspections be done every 2 years. Remarkably, there is no Law dictating how often the FDA must inspect foreign drug manufacturers, even though foreign firms pose just as great, if not greater, risk to the public health than domestic firms.

In a petition to the FDA, the Synthetic Organic Chemical Manufacturers Association, who will testify today, noted, "Foreign facilities in general pose a greater risk to public safety because when a facility is inspected infrequently, as is the case for foreign manufacturers, there is a natural tendency for management to become complacent that what was adequate at the last inspection is still adequate. Maintaining regulatory compliance requires constant effort and vigilance. Minor deviations may not cause any apparent lack of quality, but it is well-paved road from one minor deviation to serious quality failures."

Twenty years ago, the drugs Americans consumed were made in the United States. Because few firms were overseas, the FDA was reasonably positioned to closely monitor drug production facilities. However, as more foreign drug producers entered the U.S. market, FDA's ability to keep pace with inspections and monitoring has become severely limited. This was particularly true when the committee last examined this matter in 2000. Through the course of that investigation, the committee found significant shortcomings in the FDA's ability to conduct foreign inspections. Back then, FDA was under-funded, over-stretched, and poorly coordinated. Among the committee's principal findings at our 2000 hearing were, FDA officials could not determine how often foreign manufacturers were being inspected. Drug makers in India and in China were inspected on an average about every 4 to 5 years, which was more than twice FDA's 2-year inspection requirement for domestic pharmaceutical manufacturers. FDA had only enough resources to inspect foreign pharmaceutical manufacturers on an average of once every 11 years. Finally, the agency's IT systems were in disarray, relying on separate 15 data systems to identify foreign pharmaceutical manufacturers, plan foreign inspection travel, track inspection results, and monitor enforcement actions.

Nearly 8 years have passed since our last hearing, and surprisingly most of the same problems plague the FDA today. For example, resources dedicated to foreign inspection have actually declined since the GAO report of 1998, while the number of foreign drug manufacturers and imports have dramatically increased. Despite more than a decade of warnings from FDA's own internal reviews, the Congress, and Government Accountability Office, FDA's IT system is still based on multiple databases which lack integration and

contain unreliable information. Due to its poor IT systems, the FDA cannot obtain reliable data to run their risk models so they can effectively allocate what limited resources it does have for inspections. FDA's IT system has made it nearly impossible to provide the GAO, this committee, or even its own FDA managers, with key data to measure ongoing resource needs.

Let me give you one example. For almost 3 months, our committee and GAO have repeatedly asked the FDA for the number of foreign firms the agency is supposed to be inspecting overseas and where they are located. For 3 months the FDA has, on 10 different occasions, provided numbers ranging from 2,100 foreign firms to 13,800 foreign firms. The database that we believe is probably the most accurate shows that about 3,000 firms are registered to ship drug products to the United States, yet the FDA's own foreign inspection risk model uses data from about 3,300 foreign firms. Another FDA database, called OASIS, which captures actual drug shipments to the U.S., now shows an even higher figure of 6,800 foreign firms. That number was revised down from 13,800 firms just last week.

Frankly, it has been nearly impossible for the committee staff to calculate what resources FDA needs, because its internal data is simply in shambles. FDA may testify today that they know with some certainty the approximate number and location of every firm that is importing drug product in the United States, but I am not convinced the FDA can accurately calculate the number of foreign firms they should be inspecting. How can we have any confidence if the FDA is truly managing the risk that may come from foreign-made drug products if the FDA does not know the exact number or location of foreign drug manufacturers? This most basic information should be available within an hour, not 3 months. I don't believe an auto dealership could survive if it was run on the IT system that said there is between 2,000 and 13,000 cars on its lot. But apparently this passes muster at the FDA, even though it involves safeguarding the U.S. drug supply.

From the limited data we have gleaned from the agency, FDA's foreign drug inspection program has serious shortcomings. For example, FDA is capable of conducting only 200 to 300 foreign follow-up inspections each year. These are inspections that, by Law, FDA attempts to do every 2 years for foreign firms. But if one assumes that at the rough estimate of 400 firms is likely around 3,000, a simple mathematic calculation would suggest the FDA can only inspect each foreign drug firm about every 13 years. One must also question whether FDA's limited resources are being properly targeted. For example, we know that China now represents the largest source of production facilities, now shipping product to the United States with more than 700 drug firms. Yet China represents a mere four percent of where FDA is spending its foreign inspection resources.

The administration believes one of the best ways to solve the FDA's lack of inspection resources is to negotiate memorandums of agreement with foreign governments, but such efforts will not overcome the lack of FDA funding for on-the-ground foreign inspections. Mutual recognition agreements of each other's inspection reports would save considerable money, but neither China nor India,

two very large producers of pharmaceutical goods, are anywhere near being ready for such agreements. Perhaps the FDA should open offices in these parts of the world, such as India and China, where many pharmaceutical firms are now located or moving their manufacturing. Astra Zeneca, to use just one example, is one of the world's largest pharmaceutical companies, and it plans on obtaining 90 percent of its pharmaceutical ingredients from China in the very near future.

The FDA does spend considerable resources in India, about 22 percent, which is a good thing. Yet it begs the question of why the administration has not engaged in open discussions with that country, as they have been attempting to do with China. This is particularly strange given that the committee staff recently visited India and met with senior officials and industry officials, who strongly encouraged the FDA to open a permanent office in India, to reduce the backlog of needed inspections.

Every year, consumers see more and more counterfeits and poorly-made drugs floating around the world. We dodged the bullet this year on tainted toothpaste, which could have made many people sick. But dozens of Panamanians weren't so lucky last year when they died from taking poisoned medicine that purportedly came from China. That can happen here, and it surely will, if we do not get a better handle on ensuring that foreign-made drugs are safe, and their plants are inspected regularly. This will require resources and significant restructuring of the program.

Chairman Dingell and I have already had legislation designed to give the FDA more resources to do its job. Moreover, we have already sent you, members, bipartisan correspondence delineating certain changes to the program that could be enacted almost immediately. We truly hope it will be sufficient to address what are truly the root causes plaguing the FDA's foreign drug inspection program and not mere window dressing. We have been here before, in 1998, and we were told by the FDA that these problems would be fixed. Unfortunately, the problems were not fixed, and we are here again. To that end, I believe we have an opportunity to fix FDA's foreign drug program before Americans are sickened or killed by contaminated imported drugs.

That concludes my opening statement, and now I would like to turn to ranking member of the committee, Mr. Whitfield, for his opening statement.

OPENING STATEMENT OF HON. ED WHITFIELD, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. WHITFIELD. Chairman Stupak, thank you very much. As we all know, this subcommittee and the Energy and Commerce Committee as a whole has had many hearings on this important issue, and today we will examine the agency's oversight of drugs and bulk drug ingredients imported into the United States.

It is quite obvious that FDA falls short in ensuring that foreign firms exporting to the U.S. market meet good manufacturing practices. In fact, the agency devotes less than one quarter of its inspection resources and one tenth of actual inspections to these foreign operations. When you consider that 80 percent of active pharma-

ceutical ingredients originate from abroad, and the volume of drug imports is expected only to grow, this is especially the case with countries such as China and India. According to reported estimates, as much as 20 percent of the finished generic and over-the-counter drugs and more than 40 percent of bulk drugs come from China and India. Some predict these two countries will double their share of U.S.-imported drug supply within 15 years. And just consider that last year, among the 714 firms in China and 410 firms in India registered with the FDA, the agency conducted only 13 and 65 inspections respectively.

As we noted with food imports, FDA remains mired in an era when most drugs were synthesized and produced in the United States, and that is simply not the case today. Lack of good quality manufacturing is a recipe for harm. A bulk drug ingredient shipment of just 50 kilograms can result in millions of tablets or capsules produced for consumption. A bulk product that contains an impurity or was synthesized improperly, something spot testing may not detect, can cause injury or death to numerous people. And I might say that, while we have concern about the manufacturing process and the active pharmaceutical ingredients coming into the country, we certainly be concerned, and should continue to be concerned, greatly so, about drug re-importation issues as well.

We have learned on this subcommittee at past hearings that FDA linked and unapproved and impure drug ingredients imported from one Chinese firm to toxic reactions that occurred in over 150 patients across America in 1998 and 1999. One must wonder how often poorly made or intentional adulterated product causes harm, but it is undetected. Past criminal investigations have identified many bad actors, such as agents for foreign firms working to bring in cut-rate drug products, and we know without adequate oversight, people and firms can take shortcuts to save money without concern of harm to others.

It is striking that FDA has made little progress in this area to reform its system, despite repeated findings by the committee and others over the years. Even when thoughtful and comprehensive plans for reform have been developed internally at FDA, somehow it does not seem to be implemented.

Mr. Chairman, there are many issues to explore this morning. We all want to know how FDA can work to build the capacity for quality in countries and firms overseas so that we can be more confident in the manufacture of foreign drugs. We all want to know what improvements are needed for FDA's information collection and risk assessment systems so that public health is protected effectively. And most importantly I know that we all want to work with Dr. von Eschenbach to make overhauling FDA's foreign inspection program and FDA's import operations a top priority. We want to provide the money, if that is what we need. If we need legislation, we want to do that. If we can help in regulations, we want to do that. And so we would just say to him, I know he is going to be testifying later, that we want to support, we want to rally behind him and his leadership to fix this problem.

Thank you, Mr. Chairman.

Mr. STUPAK. Mr. Burgess, for opening statement, please.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman. I appreciate you holding this series of hearings because we are finding ourselves yet on the brink of one more problem, dealing with imports to our country. This time, the focus is a little bit different, but the story line is exactly the same as it has been over and over again all summer. This committee has spent a great deal of time over the past months discussing the safety and security of imported products, and we have learned our Federal agencies that are tasked with keeping America safe from harmful food or products are often using 20th-century tools or possibly even 19th-century tools when dealing with a 21st-century problem. The Food and Drug Administration does not shoulder all of the blame in this situation. As I continue to study the problem, as the committee continues to study the problem, it becomes more and more convincing that a lot of people, including people in the United States Congress, actually could not have anticipated the exploding number of imports that we have seen over the past 10 years.

Quite frankly, our Laws and regulations were never meant to handle the ever increasing number of foreign products entering into our ports. This doesn't absolve us from guilt. It just means that, as the former Speaker of the House, Mr. Newt Gingrich, so often says, real change requires real change. Now, as a doctor, I think it is important that we spend some time today discussing medicine and medicines. Medicine is supposed to heal patients, not harm them. Before I took the oath of office to become a member of the United States Congress, I first swore an oath to my profession to first do no harm. Yet how can we do no harm if we don't know what is in the medicines that are coming from what is supposedly a safe and regulated country?

It has been estimated that more than 80 percent of the active ingredients in medicines come from overseas, and about half of that comes from India and China. China, Mr. Chairman, this is the same country that manufactured over 60 percent of all the Consumer Product Safety recalls, including 90 percent of the recalled toys. Like many other Americans, I am now regarding the label, made in China, as warning, consume at your own risk. While the 20- to 40-percent number is disturbing, analysts predict that 80 percent of the active ingredients will come from China and India within the next 15 years. If this is true, then our action here today and in subsequent hearings is critical.

We must help to move the Food and Drug Administration into a 21st-century agency that can handle these 21st-century problems. And it is not just money alone that will solve the problems. We do need real reform. In fact, you can argue we need to go beyond reform. It is not just changes at the margin. It is time for real transformation. Now, at the last Oversight and Investigations hearing on food safety, I discussed the quality control with the witness from Tyson's Chicken. You may remember. He informed the committee that, yeah, they did find problems with things that were coming into their plants from suppliers in the country where they were operating, within China. And when they found those problems they dealt with them internally, but they didn't tell anybody else. They

are under no obligation to self-report any problems that they encounter with shippers, with other manufacturers, with other shippers, or even the Federal agency charged with protecting the health and safety of American citizens.

Today I hope that the witnesses will speak to this issue. Mr. Chairman, before I yield back, I would be remiss if I didn't make a couple of observations about the witnesses before us today. Certainly I want to thank Mr. William Hubbard for appearing before us today. Dr. Hubbard has appeared before us in the past and has inspired at least me to introduce legislation based on testimony that he has given to our committee, so I thank you for being with us today, and I hope you can continue to shed some light upon the solutions that are needed to fulfill the organization's own mission of building a stronger Food and Drug Administration.

And, of course, Dr. von Eschenbach is with us again today, and we are grateful that he has given his time. Honestly, Mr. Chairman, Dr. von Eschenbach is the head of a major Federal agency. His time is extremely valuable, and I know you would like to keep him in the audience so he can listen to your penetrating and probing questions, but at the same time he does have other duties to perform.

We have tasked the FDA with transformation. We have tasked the FDA with keeping us safe, and yet as I sit here this is the third Food and Drug administrator that we have had since I came to Congress a very short time ago. He has an agency to get up to speed, to get up to 21st-century functioning. Yet he can scarcely perform that arduous task that we have set before him if he spends day after day after day listening to us pontificate from the dais. He could watch us on C-Span in between the activities that he needs to do at his agency. I hope in the future when Dr. von Eschenbach is called to testify we will afford the courtesy of allowing him to go early in the day as opposed to late in the day. I do realize that we do all ask very entertaining and probing questions, but I know Dr. von Eschenbach has a lot of other things he could be doing. I for one certainly appreciate the time that he has given, the courtesy he has shown this committee. He has never complained about this issue, but I find it undignified that the committee would behave in such a way.

I do know that the FDA does require additional resources. At the same time, just this past year, when we reauthorized the Food and Drug Administration, it wasn't just the reauthorization of PDUFA and MDUFA, we made some basic changes as to how data is handled at the FDA. This is going to take us to the cusp of the 21-century type of transformation that we all need. I hope we are not a hindrance in that process, and I will yield back the balance of my time.

Mr. STUPAK. Ms. DeGette, for opening statement.

Ms. DEGETTE. Chairman, I have a brilliant opening statement that I would like to submit for the record and in the interest of having extra time for questioning.

[The prepared statement of Ms. DeGette follows:]

House Energy & Commerce Subcommittee on Oversight and Investigations
"FDA Foreign Drug Inspection Program: A System at Risk."
Opening Statement: Congresswoman Diana DeGette
November 1, 2007

Mr. Chairman, thank you for holding this very important hearing on prescription drug import safety. This hearing dove-tails nicely with the other drug and product safety issues that we have addressed recently; but in the context of the FDA's ability to inspect foreign drug manufacturing.

As you know, drug safety is very important to me, particularly surrounding drug importation and counterfeiting. Despite the fact that the issue at hand today surrounds *legitimate* drug manufacturing, not counterfeit drugs, the same safety concerns are present. Because of technological limitations, drugs are not routinely tested in a complete and thorough manner when they enter the country. Furthermore, what is to guarantee that end-product testing is a fail proof way to determine continued product safety? It is FDA's responsibility to monitor the safety and efficacy of drugs over the course of the entire manufacturing process through regular site inspections.

It is generally accepted that in order to maintain the quality of a particular drug, periodic follow-up inspections are critical. I was shocked to learn that for each overseas facility that exports drugs to the United States, FDA is able to complete an inspection only once every 8 to 12 years. Yet, Good Manufacturing Practices govern that on-site inspections should occur every two years. FDA must inspect domestic facilities every two years—why should

the standard be so much lower for foreign drugs than domestic drugs when they are consumed by the same population?

Resources are limited and more and more facilities are manufacturing drugs that will eventually end up in the U.S. pharmaceutical supply. It seems as though we are dealing with both issues surrounding end-product testing and issues surrounding systematic inspection of the manufacturing process—neither of which is currently able to satisfactorily guarantee drug safety.

GAO identified these same concerns over a decade ago, yet the FDA is still plagued by many of the same problems. I look forward to hearing from our witnesses today about the challenges the FDA currently faces in monitoring drug safety overseas and what changes we can make in order to more effectively protect our drug supply and our nation's health.

I yield back the balance of my time.

Mr. STUPAK. Very good. Mr. Murphy, I believe, is next.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF PENNSYLVANIA

Mr. MURPHY. Thank you, Mr. Chairman, and thank you for holding this hearing, which is a critically important issue we are dealing with. The American public's confidence in any products made in some foreign countries, particularly in China, is probably at rock bottom, and even this morning as I have been watching ABC Good Morning, America, they tested 100 popular children's toys. Although they found 90 of them had no lead levels of problems, still, 10 of them did and got by Federal inspectors. Yet when it comes to children's toys and when it comes to drugs, I think the American people should have zero tolerance for any kind of weakening of inspections or standards.

Although plants in the United States must be inspected regularly every 2 years, we are not yet there for some other pharmaceutical manufacturers around the world. And, as China is among them, we must be concerned and want to hear everything that our government is doing to help make sure that such plants are inspected and are meeting top standards, particularly because as we also see many factories around the world, unfortunately in China, India, and others in other small countries are involved with a great deal of counterfeiting drugs, where not only are drugs being marketed as having active ingredients when they have absolutely no active ingredients in them or may actually have poisons in them or lead paint, et cetera. This is an intolerable situation, and we, of course, all share our concern that would any of these ever be marketed or sent out through Internet sites and other marketing mechanisms as if they are legitimate drugs, with all of the stamps and other procedures on them to make them look like they are real. The FDA is in a critically important position here, and with this committee's oversight of looking at that, we are hoping to hear about the significant steps being taken to protect the American public. We want any breaches in this exposed. We want anybody who is involved in cutting any corners disciplined for that. It is something that this committee or Congress simply cannot tolerate when it comes to medications that are supposed to make things better. We cannot tolerate any system that is using counterfeiting or cutting corners that makes people sicker.

So I applaud the actions of this committee in moving forward in this. I look forward to hearing the testimony about what is being done to make sure this area is made safe. And I yield back.

Mr. STUPAK. Thank you, Mr. Murphy. Mr. Ferguson, for opening statement.

OPENING STATEMENT OF HON. MIKE FERGUSON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. FERGUSON. Thank you, Mr. Chairman. Thank you, Mr. Whitfield and the members of the subcommittee and our witnesses, for being here to discuss what many of us know is a very important issue, the safety and the security of our nation's drug supply. I am pleased that we are again addressing this critical issue in this sub-

committee. We have had several hearings in recent months on all aspects of drug safety. My biggest concern, and I think that of others on this subcommittee, is ensuring that the safety of the drug supply for our constituents and for all Americans. It is my hope that our witnesses today will be able to provide us with insights into why there seem to be gaps in the security of imported drugs into America.

Most of you have probably the New York Times article from yesterday, and if you have I am sure you are as alarmed as I am about what was contained in that. It is paramount that the citizens of this country have faith in the Federal Government's ability to monitor and ensure the safety of all of our drugs, and we know from recent investigations that they don't have good reason to have faith in that process, and perhaps not as much faith as they used to have. Many facilities have not been inspected. Other companies are using loopholes to get adulterated ingredients into the supply chain. However, the majority of ingredients used in the production of drugs are coming from outside of the U.S.

This globalization of the drug manufacturing industry is putting a strain on the FDA and their efforts to ensure the safety and the security of our drug supply. There are thousands of facilities producing finished drugs and/or ingredients around the world today creating products that will end up being ingested by Americans across our country. The GAO has been tasked with finding the deficiency in the safety and security of the drug manufacturing pipeline. Their investigations revealed that the FDA isn't completely certain as to how many foreign manufacturing facilities are even subject to inspection.

Using a risk-based assessment of the number of facilities subject to inspection, the FDA comes up with the number 3,249. However, this risk-based assessment is processed off an unverified database. At the agency's current rate of inspections it would take 13 years to inspect all of these facilities. This is with the stipulation that no new facilities be added to the list in the meantime. Even more alarming is the fact that the Federal Government doesn't have one interoperable database of manufacturing facilities, both foreign and domestic, which are willing to register and be inspected. We have three different databases for three different purposes, the drug registration and listing system for registration purposes, the field accomplishments and compliance tracking system for completed inspection information, and the operational and administrative system for import support for information on drugs and other regulated substances being imported.

If our government doesn't have a handle on the good actors, the responsible actors, how can DHS and FDA and Customs work to prevent adulterated or counterfeit drugs from entering our supply chain from the bad actors? I am pleased to say that I am going to be an original co-sponsor of Mr. Boullier's legislation when he introduces it. I want to commend Mr. Boullier. He has done an enormous amount of work on this issue. He has been a leader on the counterfeit drug issue. He has invested a lot of time and effort in the issue, and I think he has come up with a very good product.

But it really drives home the point, if we can't regulate the good actors that are playing by the rules in this industry, how are we

ever going to ensure the safety of the drug supply of other drugs coming into America? The GAO's information is very alarming, and I really think it drives home the point that preventing the importation of drugs into our supply chain, which can create safety and security problems, we have some on this committee and in this Congress who want to kick open the doors, kick open the flood gates of any drugs coming into this country, and they say, well, it is only from Canada or a country that we know of. We know for a fact that Canada and other so-called safe countries with safe drug supplies are really acting as a post office for drugs coming into this country from any place in the world. It is irresponsible, and it is wrong. We know the struggles we are having with just ensuring the drug supply of the responsible actors of products coming into this country. How in the name of God can we make sure the drug supply is safe if we are going to kick open the flood gates to any and all actors? It is the wrong way to go.

I hope we will be able to address these and other issues in the coming weeks. I look forward to hearing the testimony of our witnesses, and I thank you again, Mr. Chairman, for having this hearing.

Mr. STUPAK. Thank you, Mr. Ferguson. Mrs. Blackburn, opening statement.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman. I thank you for calling the hearing to examine this foreign drug inspection program. The inadequacies of our food and drug import system have been widely reported during the past year, and you have had the New York Times article referenced several times already today. There is a serious problem. We all recognize that. Given that the U.S. imports 80 percent of the active drug ingredients, it is critical that the Federal Government improve its drug monitoring safety system to ensure that the U.S. drug supply remains the safest in the world.

The volume of FDA-regulated pharmaceutical imports doubles every 5 years and will continue to increase. How much weight can American consumers give to the label, FDA regulated, when the FDA cannot perform timely safety inspections? When the agency fails to enforce action against foreign manufacturers and lacks the tools to monitor foreign drug manufacturers, how can Americans feel safe? If American drug manufacturers are required to follow the letter of the Law regarding FDA drug safety inspections, Congress should expect nothing less from foreign manufacturers. Foreign manufacturers must play by the same rules that our domestic manufacturers follow.

If consumer safety is priority number one, and it should be, then we have a lot of work to do to ensure that this goal is going to be met. It is worth noting, however, that many of the voices calling for an overhaul of the U.S. drug safety inspection system concurrently called for legislation that would import prescription drugs from other nations. Drug re-importation fails to ensure the high safety standards that Americans have come to expect. Americans

clearly do not need a flood of unsafe prescription drugs finding their way into the medicine cabinets across this country, especially since there is no guarantee of quality or that imported medication is indeed safe for us.

When someone gets that imported drug, and it turns out to be unsafe, we have another public health threat on our hands. This subcommittee has examined drug import safety in numerous hearings during the 110th Congress, and the record shows that it is unrealistic for the FDA to inspect all imports coming into the United States. However, Americans demand greater accountability in the nation's drug supply through considerable and expedient improvement of the FDA's current drug safety review system.

I look forward to the testimony today from our witnesses, and I yield back the balance of my time.

Mr. STUPAK. Thank the gentlelady. Seeing no other members, we will call our first panel to come forward. Dr. Marcia Crosse, the Director of the Public Health and Military Health Care Issues at the United States Accountability Office; Mr. William Hubbard, former senior FDA employee and current Senior Advisor to the Coalition for a Stronger FDA; Mr. Ben England, former senior FDA employee and current Special Counsel at Jones, Walker, et al. law firm; and Mr. Carl Nielsen, retired Director of the Division of Import Operations within the Office of Regulatory Affairs at the FDA.

It is the policy of this subcommittee to take all testimony under oath. Please be advised that witnesses have a right under the rules of the House to be advised by counsel during their testimony. Do any of you wish to be represented by counsel? Seeing none of you wish to, then I am going to swear you in, but then I am going to have Mr. Dingell give an opening statement if he so wishes. So please raise your right hand.

[Witnesses sworn]

Mr. STUPAK. Let the record reflect that each witness answered in the affirmative, and they are now all under oath. Mr. Chairman, would you like to make an opening statement at this time?

Mr. DINGELL. Mr. Chairman, you are most gracious. This is deja vu all over again. I have a fine opening statement. I am sure everybody is familiar with it. It is something very much identical to what has been given for years, and I don't want to deter you in your good work. I commend you for what you are doing. I thank you for your gracious kindness to me. I urge you to continue your vigorous effort in this matter, and we are going to try and make the American people safe from some of these imported pharmaceuticals and imported foods that are putting their lives at risk.

Thank you, Mr. Chairman.

[The prepared statements of Messrs. Dingell and Barton follow:]

STATEMENT
OF
THE HONORABLE JOHN D. DINGELL
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
HEARING ON "FDA FOREIGN DRUG INSPECTION PROGRAM: A SYSTEM AT RISK"

NOVEMBER 1, 2007

Mr. Chairman, today's hearing could not be timelier given the unremitting bad news regarding the safety of imported products. I am struck, however, by how little has changed in the seven years since our last hearing on the Food and Drug Administration (FDA) foreign drug inspection program—it's like *déjà vu* all over again.

Seven years ago, this Subcommittee heard FDA Commissioner Jane Henney testify that:

- FDA could not provide a complete list of foreign drug producing facilities;

- FDA lacked an information technology (IT) system able to effectively manage the foreign drug inspection program; and

- FDA lacked the resources to inspect foreign drug manufacturing firms that imported to the U.S. at the recommended two-year intervals, as is required for domestic companies.

Mr. Chairman, you may think you are hearing an echo in the room, but let me summarize today's findings:

- FDA still cannot calculate the number of foreign drug producing facilities shipping products into the U.S.;

- FDA's IT system still is as broken as it was back then, unable to provide critical data for regulating foreign drug production; and

- FDA still lacks the necessary resources to effectively conduct foreign inspections to ensure that the medicines made abroad are safe for U.S. consumers.

There is one slight change since our last hearing. Unfortunately, it is a change for the worse. Despite the dramatic increases of drug imports into the U.S.—indicating even more foreign drug facilities requiring inspection—the agency's resources have actually decreased since our last hearing.

I believe that the American people generally assume that the FDA ensures that foreign-manufactured drugs sold in this country are safe. They assume incorrectly.

For example, most experts recommend that drug-producing firms be inspected about every two to three years, which is generally how often domestic drug firms by law are required to be inspected. The rules for foreign firms, however, are completely different.

According to testimony we will hear today, FDA only has the resources to inspect foreign firms once every 13 years on average. China, for example, now has more facilities manufacturing drug products for the U.S. market than any other country, some 714.

Yet given the FDA's anemic resources, only 13 inspections were conducted in China in 2007. At this rate, it would take the FDA 55 years just to clear this backlog.

The bottom line is that the FDA has no clue what the condition is of most foreign drug-manufacturing facilities that import into the U.S. market. The agency is using an antiquated regulatory system from the last century, when the global economy was very different. It is time that FDA both receives and dedicates enough resources so as to effectively carry out its mission in today's global market.

Mr. Chairman, I have introduced a bill that will give FDA adequate resources to do its job. I hope the Members of this Committee will work together on this legislation to see to it that it becomes enacted into law. This hearing should serve as a wake-up call to FDA that it's time to seriously address the restructuring and funding the foreign drug inspection program. Nothing less will restore the confidence of the American people in the safety and efficacy of our drug supply.

Opening Statement of the Honorable Joe Barton
Ranking Member, Committee on Energy and Commerce
For
Subcommittee on Oversight and Investigations Hearing:
"FDA Foreign Drug Inspection Program: A System at Risk"
November 1, 2007

Chairman Stupak and Ranking Member Whitfield, thank you for holding this hearing. Thank you for continuing the Committee's bipartisan oversight of the Food and Drug Administration's foreign drug inspection program. Americans are anxious about the safety of imported products, especially the medicine we take with ingredients from China or India. People are right to be worried, because those are two countries with a history of counterfeiting and sloppy manufacturing. Americans want facts, they want answers, and they want the Federal government to ensure that the medicines people take to make them well are not making them sick.

More and more drugs and drug ingredients come from overseas. And more and more come from China and India. These trends are expected to continue over the next five years. FDA's foreign drug inspection program and FDA's import programs are responsible for overseeing these imports.

Today, we will hear that the FDA is struggling to meet these responsibilities, and that the FDA lacks the data to determine whether it is effectively assessing and reducing the risks of foreign drug imports. For example, we have learned:

- That FDA does not know how many foreign firms are making drug product shipped to the United States;
- That FDA does not know how many foreign firms are shipping drug products to the U.S.
- That FDA does not know how many Chinese firms sell ingredients used in drugs consumed by Americans.

Mr. Chairman, ignorance is almost never bliss. What you don't know can hurt you. According to past testimony from FDA before this Subcommittee, drugs of unknown origin and quality pose a potential health hazard. The fact that the manufacturing is unknown means there is no product history. Therefore, we do not know if the product is safe or whether it works. We don't know the impurity profile, how it was stored, the manufacturing environment, and how the product was synthesized.

The agency does not even know the size of the problem it is tasked with managing. When you don't know what you're measuring, you're

probably not measuring things that need to be measured and you can't tell what you're doing is even effective. And right now, this shot-in-the-dark science is all that stands between Americans and some truly bad medicine.

To be fair, FDA has lacked resources in the import program for some time. But after 9-11, there was supposed to be a resource boost to the import program and attempts were made to create a new import strategy for FDA. The bottom line, though, is that FDA's strategy and use of resources has not fundamentally changed since the Subcommittee looked at this issue when I was the Chairman a decade ago. The only difference is that things seemed to have gotten worse: the volume of drug imports continues to increase, while the resources decrease.

They say the definition of insanity is doing the same thing over and over, but expecting different results. Even though drug imports have skyrocketed, FDA continues with basically the same databases, the same limited knowledge, the same strategy, and the same secondary status for the foreign inspection program compared to the domestic inspection program. FDA needs more resources, but it also needs a new strategy and a new approach.

Commissioner von Eschenbach, you have a chance to be a hero. This is your moment in history. You have met with Committee staff, met with the Chinese government, and met with other stakeholders. You're working with the President's Import Working Group. I stand ready to give you the support you need to heroically improve FDA's interception of tainted drugs from abroad.

We just aren't living in the 20th century world where almost all drug products were made in the USA, and we aren't going back. As we go forward, FDA needs to get more and better data so it can assess real risks. FDA also needs a separate foreign inspection program, with an adequate number of inspectors and investigators assigned to it full-time. In the 21st century, foreign inspections cannot continue to be the neglected stepchild of FDA's domestic operations.

I welcome the witnesses and especially Commissioner von Eschenbach. I look forward to the testimony, and more importantly, look forward to helping FDA make real progress on drug imports.

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Mr. STUPAK. Thank you, Mr. Dingell. Dr. Crosse, if you would, we would start with you for an opening statement, please. A longer version will be submitted for the record, so please try to limit your testimony to five minutes. Dr. Crosse.

TESTIMONY OF MARCIA G. CROSSE, DIRECTOR, PUBLIC HEALTH AND MILITARY HEALTH CARE ISSUES, U.S. GOVERNMENT ACCOUNTABILITY OFFICE

Ms. CROSSE. Thank you, Mr. Chairman, and members of the subcommittee. I am pleased to be here today as you examine FDA's inspections of foreign drug manufacturers. As you know, the United States increasingly relies on drugs manufactured in other countries. Slide, please.

[Slide]

As you can see in this figure, there are firms in more than 50 countries that are registered to manufacture drugs for the U.S. market, with the heaviest concentration in China and India, as we have heard. The FDA is responsible for overseeing the safety and quality of human drugs sold in the United States, whether they are manufactured in foreign or domestic establishments. As part of its efforts to ensure the safety and quality of imported drugs, FDA is responsible for inspecting foreign establishments to ensure that they meet the same quality standards required of domestic establishments. For domestic establishments, FDA's usual approach is to conduct surveillance inspections of good manufacturing practices to ensure that marketed drugs continue to be manufactured in compliance with standards. FDA is required to conduct such inspections every 2 years for domestic establishments, but there is no comparable requirement for inspecting foreign establishments.

We reported in 1998 that FDA needed to improve its foreign drug inspection programs. Today, almost a decade later, questions remain about FDA's ability to oversee foreign drug establishments and whether FDA has improved its management of the foreign drug inspection program. My remarks provide preliminary information on the review we are conducting at your request. Today I will discuss the extent to which FDA has accurate data to manage the foreign drug inspection program, the frequency of foreign inspections, and factors influencing the selection of establishments to inspect, and certain issues that are unique to conducting foreign inspections.

We are finding that FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by substantial weaknesses in its databases. FDA does not know how many foreign establishments are subject to inspection. Because of this, FDA does not have adequate information on the full scope of their responsibilities, which limits their ability to appropriately manage. Instead, FDA relies on databases that were designed for other purposes and contain inaccuracies that FDA cannot easily reconcile. Slide, please.

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For example, one of the databases indicates there are about 3,000 establishments registered to import drugs into the United States, while another indicates that about 6,800 foreign establishments actually imported drugs in the past year. However, despite

the more than two-fold different in the estimates of foreign establishments, FDA does not verify the information within each database. For example, the agency does not confirm that a registered establishment actually manufactures a drug for the U.S. market. Similarly, FDA has not generated an accurate listing of the establishments whose drugs have actually been imported into the United States. Slide, please.

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At a time when manufacturing of drugs for the U.S. market is increasing in foreign countries, FDA's inspections have not kept pace. FDA inspects relatively few foreign establishments. Data used by FDA to prioritize foreign establishments for inspection suggests that the agency may inspect about seven percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that the rate of inspections remains constant and that no additional establishments require inspection. Slide, please.

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The mismatch between the number of inspections performed and the number of establishments subject to inspection appears to be the largest in China. Further, FDA cannot provide an exact number of foreign establishments that have never been inspected. But, according to FDA's data, it may be more than 2,000, and the largest number of such establishments are also likely to be in China. Slide, please.

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FDA's foreign inspection process is driven by the current statutory and regulatory requirements for timely review of applications to market new drugs. Among the limited number of foreign inspections, most are pre-approval inspections conducted as part of the processing of a drug application to allow a manufacturer to begin marketing a particular drug in the United States. In the last 6 years, 88 percent of FDA's inspections of foreign inspections involved such pre-approval inspections. Although FDA uses a risk model to develop a prioritized list of foreign establishments for surveillance inspections, to ensure continued compliance, few such inspections are completed in a given year. This prioritized list was used to select about 30 foreign establishments for inspection in fiscal year 2007, and 50 are targeted for inspection in fiscal year 2008. Further, FDA coordinates these relatively few surveillance inspections with travel to locations for pre-approval inspections to make efficient use of travel funds. The need to coordinate travel is a bigger factor in the selection of foreign establishments than FDA's risk model. Slide, please.

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This is in marked contrast to the pattern of domestic inspections. About 78 percent of FDA's inspections of domestic establishments were specifically for the purpose of a surveillance inspection, to ensure that manufacturers continue to comply with good manufacturing requirements. The comparable figure for foreign establishments is 12 percent. Further, in the last 6 years, FDA has conducted almost seven times as many inspections domestically as abroad. And this is for about an equal or smaller number of establishments. Slide, please.

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Finally, the foreign inspection process also involves unique circumstances that are not encountered domestically. For example, FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections, FDA does not arrive unannounced at a foreign establishment. It also lacks the flexibility to easily extend foreign inspections if problems are encountered because of the need to adhere to an itinerary that typically involves multiple inspections in the same country. In addition, language barriers can make foreign inspections more difficult than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected rather than an independent translator. Slide, please.

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In conclusion, our preliminary work indicates that fundamental flaws that we identified in the management of this program in 1998 continue to exist. FDA still does not have a reliable list of foreign establishments that are subject to inspection. As more imported drugs enter the United States, it becomes increasingly important that foreign establishments receive appropriate scrutiny. However, until FDA responds to systemic weaknesses in the management of this important program, it cannot provide the needed assurance that the drug supply reaching our citizens is appropriately scrutinized and safe.

Mr. Chairman, this concludes my prepared remarks. I would be happy to answer any questions that you or other members of the subcommittee may have.

[The prepared statement of Dr. Crosse follows:]

United States Government Accountability Office

GAO

Testimony

Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

For Release on Delivery
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DRUG SAFETY

Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

Statement of Marcia Crosse, Director
Health Care

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Highlights

Highlights of GAO-08-224T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

November 1, 2007

DRUG SAFETY

Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

Why GAO Did This Study

Many drugs marketed in the United States are manufactured in foreign countries and the value of such products entering the country is increasing. The Food and Drug Administration (FDA) is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments. Foreign establishments that market their drugs in the United States must register with FDA and FDA inspects foreign establishments to ensure that they meet the same standards that are required of domestic ones. GAO reported 9 years ago that FDA needed to improve its foreign drug inspection program (GAO/HEHS-98-21). Questions remain as to whether FDA has improved its management of the foreign drug inspection program.

This statement discusses preliminary information on (1) the extent to which FDA has accurate data to manage the foreign drug inspection program, (2) the frequency of foreign inspections and factors influencing the selection of establishments to inspect, and (3) issues unique to conducting foreign inspections. To address these issues GAO interviewed FDA officials; reviewed pertinent statutes, regulations, and guidance; and analyzed information from FDA databases. Because of the preliminary nature of our work, we are not making recommendations at this time.

To view the full product, including the scope and methodology, click on GAO-08-224T. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its databases. FDA does not know how many foreign establishments are subject to inspection. Instead, FDA relies on databases that were not designed for this purpose. Further, these databases contain inaccuracies that FDA cannot easily reconcile. One database indicates there were about 3,000 foreign establishments registered to market drugs in the United States in fiscal year 2007, while another indicates that about 6,800 foreign establishments actually imported drugs in that year. FDA recognizes these flaws. Further, because the databases cannot exchange information, any comparisons of the data are performed manually, on a case-by-case basis. FDA officials told GAO that they have not generated an accurate count of foreign establishments whose drugs are imported into the United States.

FDA inspects relatively few foreign establishments. Data from FDA suggest that the agency may inspect about 7 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that no additional establishments require inspection. However, FDA cannot provide an exact number of foreign establishments that have never been inspected. Most of the foreign inspections performed are conducted as part of a review associated with processing an application to market a new drug, rather than inspections for monitoring the quality of marketed drugs. Although FDA uses a risk-based process to develop a prioritized list of foreign establishments for inspections to monitor the quality of marketed drugs, few are completed in a given year. This prioritized list was used to select foreign establishments for inspection in fiscal year 2007. According to FDA, about 30 such inspections were completed in that year and at least 50 are targeted for inspection in fiscal year 2008.

The foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections to monitor the quality of a marketed drug, FDA does not arrive unannounced at a foreign establishment. It also lacks the flexibility to easily extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country. Finally, language barriers can make foreign inspections more difficult than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you examine the Food and Drug Administration's (FDA) inspections of foreign drug manufacturers whose products are imported into the United States. In 1998, we reported that FDA needed to improve its foreign drug inspection program.[1] Among other things, we noted that FDA had serious problems managing its foreign inspection data and that it lacked a comprehensive automated system for tracking this important information. We were also critical of the number of inspections FDA conducted at foreign manufacturers. At that time, FDA reported on our growing dependence on imported pharmaceutical products, noting that as much as 80 percent of the bulk drug substances[2] used by manufacturers in the United States to produce prescription drugs was imported and that the number of finished drug products manufactured abroad for the U.S. market was increasing. Today, we are still dependent on foreign establishments[3] manufacturing drugs for the U.S. market as the value of pharmaceutical products coming into the United States from abroad continues to increase.[4]

Given the importance of FDA's foreign drug inspection program, you expressed concern about FDA's ability to oversee foreign establishments manufacturing drugs and asked whether FDA has improved its management of the foreign drug inspection program since our previous report was issued. My testimony today will summarize preliminary findings from our ongoing work to update our 1998 report. My remarks will focus on (1) the extent to which FDA has accurate data to manage its foreign drug inspection program, (2) the frequency of foreign inspections and factors influencing the selection of establishments to inspect, and (3) issues unique to conducting foreign inspections.

[1]GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, GAO/HEHS-98-21 (Washington, D.C.: Mar. 17, 1998).

[2]A bulk drug substance is any substance that is represented for use in a drug that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished drug product. 21 C.F.R. § 207.3(a)(4)(2007).

[3]FDA regulations define an establishment as a place of business under one management at one general physical location. 21 C.F.R. § 207.3(a)(7)(2007). Drug firms may have more than one establishment.

[4]According to GAO analysis of International Trade Centre data, the value of pharmaceutical imports increased 42 percent from 2001 to 2005 adjusted for pharmaceutical inflation. The International Trade Centre is a joint agency of the United Nations Conference on Trade and Development and the World Trade Organization.

To address these issues, we interviewed officials from FDA's Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing the foreign drug inspection program. We reviewed pertinent statutes and regulations as well as agency documents that provide guidance on conducting inspections and provide the basis for FDA's assessment of an establishment's compliance with current good manufacturing practices (GMP).[5] These documents included FDA's Compliance Program Guidance Manuals, its Guide to Inspections of Foreign Pharmaceutical Manufacturers, and its Investigations Operations Manual 2007. We also obtained information from FDA databases on establishments whose drugs have been imported into the United States. Specifically, we obtained data from the Drug Registration and Listing System (DRLS), the Field Accomplishments and Compliance Tracking System (FACTS), and the Operational and Administrative System for Import Support (OASIS). We assessed the reliability of these data by (1) reviewing existing information about the data and the databases that produced them, (2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of data elements from FACTS. We found the data in the FACTS database reliable for our purposes. We also found that DRLS was reliable, to the extent that it accurately reflects information provided by foreign establishments that register to market drugs in the United States. However, we determined that these data do not necessarily reflect all foreign establishments whose drugs are imported into the United States. In addition, we found that OASIS is likely to over-estimate the number of foreign establishments whose drugs have been imported into the United States, due to uncorrected errors in the data. Therefore, we present information from both DRLS and OASIS to illustrate the variability in information that FDA's databases provide to agency officials on this topic. This represents the best information available and is what FDA relies on to manage its foreign drug inspection activities. Our ongoing work is focused on human drugs regulated by CDER and not on biologics,[6] medical devices, veterinary medicines, or other items or products for which FDA conducts inspections. We received technical comments on a draft of this statement from FDA, which we incorporated as appropriate.

[5]GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality products. See 21 C.F.R. pts. 210, 211 (2007).

[6]Biologics are materials, such as vaccines, derived from living sources such as humans, animals, and microorganisms. Some biologics are regulated by CDER and inspections related to those products are included in our work.

Our work is being performed in accordance with generally accepted government auditing standards.

In summary, our preliminary results indicate that more than 9 years after we issued our last report on this topic, FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its data systems. FDA does not know how many foreign establishments are subject to inspection. FDA relies on information from several databases that were not designed for this purpose. One of these databases contains information on foreign establishments that have registered to market drugs in the United States, while another contains information on drugs imported into the United States. One database indicates about 3,000 foreign establishments could have been subject to inspection in fiscal year 2007, while another indicates that about 6,800 foreign establishments could have been subject to inspection in that year. Despite the divergent estimates of foreign establishments subject to inspection generated by these two databases, FDA does not verify the data within each database. For example, the agency does not routinely confirm that a registered establishment actually manufactures a drug for the U.S. market. However, FDA used these data to generate a list of 3,249 establishments from which it prioritized establishments for inspection.

Because FDA is not certain how many foreign establishments are actually subject to inspection, the percentage of foreign establishments that have been inspected cannot be calculated with certainty. We found that FDA inspects relatively few foreign establishments. Using the list of 3,249 establishments from which FDA prioritized establishments for inspection, we found that the agency may inspect about 7 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment on this list once, assuming that no additional establishments are subject to inspection. FDA cannot provide the exact number of foreign establishments that have never been inspected. Most of the foreign inspections are conducted as part of processing a new drug application (NDA) or an abbreviated new drug application (ANDA),[7] rather than as GMP surveillance inspections, which are used to monitor the quality of marketed drugs. Although FDA used a risk-based process to develop a prioritized list of foreign establishments

[7]FDA must approve an NDA in order for a new drug product to be marketed in the United States; approval for a generic drug is sought through an ANDA. FDA also reviews scientific and clinical data contained in these applications, as part of its process in considering them for approval to be marketed.

for GMP surveillance inspections in fiscal year 2007, few such inspections are completed in a given year. According to FDA, about 30 such inspections were completed in fiscal year 2007 and at least 50 are targeted for inspection in fiscal year 2008. Further, the data on which this risk-based process depends limits its effectiveness.

Finally, the very nature of the foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA does not have a dedicated staff to conduct foreign inspections and relies on those inspecting domestic establishments to volunteer. While FDA may conduct unannounced GMP surveillance inspections of domestic establishments, it does not arrive unannounced at foreign establishments. It also lacks the flexibility to easily extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country. Finally, language barriers can make foreign inspections more difficult to conduct than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

Because of the preliminary nature of our work, we are not making recommendations at this time.

Background

FDA is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments.[8] Foreign establishments that market their drugs in the United States must register with FDA. As part of its efforts to ensure the safety and quality of imported drugs, FDA is responsible for inspecting foreign establishments whose products are imported into the United States. The purpose of these inspections is to ensure that foreign establishments meet the same manufacturing standards for quality, purity, potency, safety, and efficacy as required of domestic establishments.

Requirements governing foreign and domestic inspections differ. Specifically, FDA is required to inspect registered domestic establishments

[8]FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. See 21 C.F.R. § 207.3(a)(8) (2007).

that have been previously approved to market their drugs in the United States every 2 years,[9] but there is no comparable requirement for inspecting foreign establishments. FDA does not have authority to require foreign establishments to allow the agency to inspect their facilities. However, FDA has the authority to conduct physical inspections of the imported product or prevent its entry at the border.

Within FDA, CDER sets standards for and evaluates the safety and effectiveness of prescription drugs and over-the-counter drugs. Among other things, CDER requests that ORA inspect both foreign and domestic establishments to ensure that drugs are produced in conformance with federal statutes and regulations, including current GMPs. CDER requests that ORA conduct inspections of establishments that produce finished drug products. CDER also requests inspections of those that produce bulk drug substances, including the active pharmaceutical ingredients (API)[10] used in finished drug products. These inspections are performed by investigators and laboratory analysts.[11] ORA conducts two primary types of inspections[12]:

- Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States. These inspections occur following FDA's receipt of an NDA or ANDA and focus on the manufacture of a specific drug product. Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications and ensures that the manufacturer of the finished drug product, as well as each manufacturer supplying a bulk drug substance used in the finished

[9]21 U.S.C. § 360(h).

[10]An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product.

[11]ORA investigators lead inspections. They are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing.

[12]FDA may also conduct other postapproval inspections, such as to address adverse events associated with a particular drug. In addition, FDA conducts for-cause inspections when it receives information indicating problems in the manufacture of approved drug products, as well as when it follows up on manufacturers that were not in compliance with GMPs during previous inspections.

product, manufactures, processes, and packs the drug adequately to preserve its identity, strength, quality, and purity.

- Postapproval GMP surveillance inspections are conducted to ensure compliance with applicable laws and regulations pertaining to the manufacturing processes used by domestic and foreign establishments in the manufacture of finished drug products marketed in the United States and bulk drug substances used in the manufacture of those products. These inspections focus on a manufacturer's systemwide controls for ensuring that drug products are high in quality. Systems examined during these inspections include those related to quality control, production, and packaging and labeling. These systems may be involved in the manufacture of multiple drug products.

FDA allocates funds to ORA to carry out preapproval and postapproval inspections of foreign and domestic establishments. ORA develops an annual work plan and a budget that estimates human resources available to conduct activities related to foreign inspections. ORA also develops estimates for inspections of domestic establishments. Typically, ORA investigators and laboratory analysts travel abroad for about 3 weeks at a time, during which they inspect approximately three establishments. Each establishment inspection typically lasts a week, with 1 day of each week set aside for documenting the inspection or for extending the inspection, if necessary.

CDER uses a risk-based process to select some domestic and foreign establishments for postapproval GMP surveillance inspections. According to an FDA report,[13] the agency developed the process after recognizing that it did not have the resources to meet the requirement for inspecting domestic establishments every 2 years.[14] The process uses a risk model to identify those establishments that, based on characteristics of the establishment and of the product being manufactured, have the greatest public health risk potential should they experience a manufacturing defect. (See table 1 for a description of the risk-based site selection model

[13]Department of Health and Human Services, U.S. Food and Drug Administration, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model," (September 2004), http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm (accessed Oct. 21, 2007).

[14]Previously, FDA used other less formal risk-based systems to prioritize its inspections. For example, we noted in our 1998 report that FDA had used a risk-based site selection system, in which it classified establishments according to risk tiers. See GAO/HEHS-98-21.

used by FDA in fiscal year 2007.) For example, FDA considers the risk to public health from poor quality over-the-counter drugs to be lower than for prescription drugs, and consequently establishments manufacturing only over-the-counter drugs receive a lower score on this factor than other manufacturers. Through this process, CDER annually prepares a prioritized list of domestic establishments and a separate, prioritized list of foreign establishments. CDER began applying this risk-based process to domestic establishments in fiscal year 2006 and expanded it to foreign establishments in fiscal year 2007.

Table 1: Summary of Factors in FDA's Risk-Based Site-Selection Mod l in Fiscal Year 2007

Category of factor	Description	Example(s)
Product	Factors pertaining to the intrinsic properties of drug products such that quality deficiencies could potentially and adversely affect public health	FDA considers establishments manufacturing prescription drugs, as opposed to only over-the-counter drugs, to be higher risk
Process	Factors pertaining to aspects of drug manufacturing operations that may predict potential difficulties with process control or vulnerability to various forms of contamination	FDA considers establishments manufacturing small-volume drugs administered intravenously to be higher risk than those manufacturing prompt release tablets, because of the greater risk of contamination associated with the manufacture of small-volume intravenous products
Facility	Factors relating to characteristics of a manufacturing site believed to be predictive of potential quality risks	FDA considers establishments that have not had a recent GMP inspection to be higher risk than those that have received a recent GMP inspection

Source: GAO analysis of FDA's risk model.

FDA relies on multiple databases to manage the foreign drug inspection program. FDA assigns unique numeric identifiers to establishments, known as the FDA establishment identifier (FEI) number. An FEI number could be assigned at the time of registration, importation, or inspection.

- DRLS contains information on foreign and domestic drug establishments that have registered with FDA. Establishments that market their drugs in the United States must register with FDA. These establishments provide information, such as company name and address and the drug products they manufacture for commercial distribution in the United States, on paper forms that are entered into DRLS by FDA.

- OASIS contains information on drugs and other FDA-regulated products imported into the United States, including information on the establishment that manufactured the drug. The information in OASIS is automatically generated from data managed by U.S. Customs and Border Protection, which are originally entered by customs brokers based on the information available from the importer.[15] Each establishment is assigned a manufacturer identification number that is generated from key information entered about an establishment's name, address, and location.

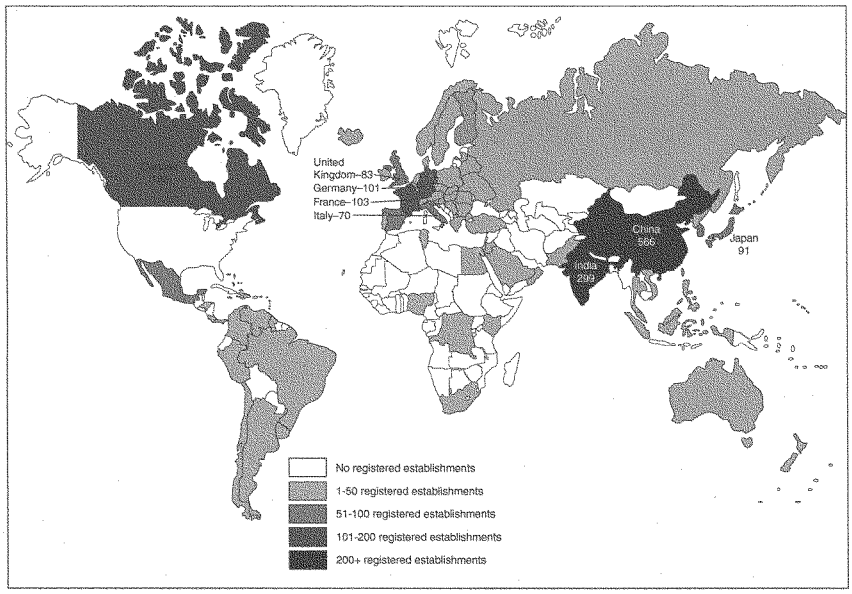
- FACTS contains information on FDA's inspections of domestic and foreign drug establishments. FDA investigators and laboratory analysts enter information into FACTS, following completion of an inspection.

According to DRLS, in fiscal year 2007, China and India had more establishments registered to manufacture drugs for the U.S. market than any other country.[16] Other countries that had a large number of establishments registered to manufacture drugs for the U.S. market in this year were Canada, France, Germany, Italy, Japan, and the United Kingdom. (See fig. 1.) These countries are also listed in OASIS as having the largest number of manufacturers importing drugs into the United States.

[15]Customs brokers are private individuals, partnerships, associations, or corporations licensed, regulated, and empowered by U.S. Customs and Border Protection to assist in meeting federal requirements governing imports and exports.

[16]These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

Figure 1: F reign Establishments Registered to Manufacture Drugs for the U.S. Market, by Country, Fiscal Year 2007



Source: GAO analysis of FDA data.

Note: These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

FDA Lacks Accurate Information to Effectively Manage the Foreign Drug Inspection Program

FDA does not know how many foreign establishments are subject to inspection; including the number of establishments that are registered and whose products are currently imported into the United States and establishments that are not required to register but whose products are ultimately used in drugs that are marketed here. Instead of maintaining a list of such establishments, FDA relies on information from several databases that were not designed for this purpose.

DRLS, established in 1991, is intended to list the establishments registered that manufacture drugs for the U.S. market. However, requirements for the registration of foreign establishments were not implemented until 2002.[17] FDA expected that requiring foreign establishments to register would provide it with a comprehensive list of such establishments. In fiscal year 2007, approximately 3,000 foreign establishments were registered with FDA that manufactured human drugs, biologics, or veterinary drugs; FDA was unable to determine from this database the number of registered establishments specifically manufacturing human drugs.

DRLS provides FDA with some information about establishments subject to inspection, but contains inaccuracies and does not provide a complete count. FDA officials told us that the count of registered foreign establishments in DRLS does not reflect the actual number whose products are being imported into the United States for several reasons. First, foreign establishments may register with FDA, whether or not they actually manufacture drugs for the U.S. market. FDA officials told us that this is made more likely by the fact that FDA does not charge foreign establishments a fee to register. FDA officials pointed out that some foreign establishments register because, in foreign markets, registration may erroneously convey an "approval" or endorsement by FDA. Second, foreign establishments may not renew their registration information, although they are required by FDA to do so annually. Agency officials told us that if foreign establishments stop manufacturing drugs for the U.S. market or go out of business they may not report the change to FDA, even though it is required. FDA officials told us that the agency does not routinely verify the information provided by the establishment to ensure that it is accurate or confirm that the establishment actually manufactures

[17]See Pub. L. No. 105-115, §§ 417, 501, 111 Stat. 2296, 2379-80. FDA issued implementing regulations in 2001, which were effective February 11, 2002. 66 Fed. Reg. 59138 (Nov. 27, 2001).

drugs for the U.S. market.[18] FDA does not know how many foreign establishments are erroneously registered. Third, foreign establishments that manufacture APIs are not required to register if their products are not directly imported into the United States.[19]

OASIS also provides FDA with some information about establishments subject to inspection, but this database contains inaccurate data on the count of foreign establishments manufacturing drugs imported into the United States. According to OASIS, 6,760 foreign establishments manufactured drugs that were imported into the United States in fiscal year 2007. However, FDA officials told us that errors in data entry result in inaccurate counts of establishments whose drugs are imported into the United States. FDA officials told us that if information about an establishment—such as its name—was entered by customs brokers incorrectly, a new manufacturer identification number, and thus a new FEI number, could be assigned to an establishment that already has an FEI number. For example, a customs broker may enter an establishment's name slightly differently from the way it is displayed in OASIS, such as using "Inc." instead of "Incorporated," which would lead to the creation of a second FEI number for the establishment. Therefore, a single establishment may be counted more than once in OASIS, which would result in an artificially high count of foreign establishments importing drugs into the United States. FDA officials acknowledge this problem but were unable to provide us with an estimate of the extent of that error. In addition, the agency does not have a process for systematically identifying and correcting these errors. To mitigate this problem, the officials told us that FDA has provided regional training to brokers as a way to improve accuracy. FDA officials also told us that the agency is pursuing a new government-wide initiative that would address this problem by providing a unique identifier for each foreign establishment involved in the import supply chain.

FDA's data suggest that between 3,000 and 6,760 establishments could be subject to FDA inspection. However, FDA officials told us that the two

[18]If the agency learns of an error, it would ask the establishment to submit corrected information.

[19]For example, an establishment in China may export an API to Germany. The German establishment may use the API in its production of a drug that is imported into the United States. Although the German establishment would be required to notify FDA of its arrangement with the Chinese establishment, and the Chinese establishment would be subject to inspection by FDA, the Chinese establishment is not required to register.

databases—DRLS and OASIS—cannot be electronically integrated or interact with one another, so any comparisons are done manually for each individual establishment. Because comparisons of the data and error identification are done manually, the databases are not conducive to routine data analysis. FDA officials told us that they have not generated an accurate count of the establishments whose drugs are imported into the United States.

Because FDA does not have a list of all foreign establishments subject to inspection, in fiscal year 2007 it created a list of such establishments for the purpose of applying its risk-based process.[26] In preparing this list, FDA draws on information from DRLS. It also obtains information from previous inspections to help it identify establishments that are subject to inspections but are not required to register—such as the manufacturer of an API whose product is not directly imported into the United States. For fiscal year 2007, this list consisted of 3,249 foreign establishments. However, as a result of the inaccuracies in DRLS, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

[26]In addition to establishments identified for the purposes of conducting its risk-based analysis, FDA also identifies establishments subject to inspection that are named in NDAs or ANDAs using its Establishment Evaluation System database. This database identifies the multiple establishments involved in drug manufacturing, including the establishments manufacturing a finished product for import into the United States and the establishments manufacturing any APIs for that finished product.

FDA Conducts Relatively Few Foreign Establishment Inspections and Relies on the NDA and ANDA Review Process as the Primary Selection Factor

FDA conducts relatively few inspections of foreign drug establishments. However, because FDA is not certain how many foreign establishments are actually subject to inspection, the percentage of foreign establishments that have been inspected cannot be calculated with certainty. Most foreign establishments are selected for inspection as part of the agency's review process associated with an NDA or ANDA. Therefore, the vast majority of foreign inspections include a preapproval inspection. In addition, although FDA has implemented a risk-based process in selecting foreign establishments for GMP surveillance inspections, relatively few such inspections are conducted. FDA tries to make efficient use of its resources by selecting establishments for these inspections that allow it to coordinate travel with preapproval inspections.

Relatively Few Foreign Establishments Are Inspected by FDA Each Year

In each year we examined, FDA inspected a small portion of foreign establishments through either preapproval or GMP surveillance inspections. However, its lack of a list of foreign establishments subject to inspection makes it difficult to determine an exact percentage. Based on our review of data on inspections, FDA conducted an average of 241 foreign establishment inspections per year from fiscal year 2002 through fiscal year 2007.[21] Comparing this average number of inspections with FDA's count of 3,249 foreign establishments it used to plan its fiscal year 2007 prioritized GMP surveillance inspections suggests that the agency inspects about 7 percent of foreign establishments in a given year. At this rate it would take FDA more than 13 years to inspect this group of establishments once, assuming that no additional establishments are subject to inspection.

FDA's data indicate that some foreign drug manufacturers have not received an inspection, but the exact number of establishments not inspected was unclear. Of the list of 3,249 foreign establishments, there were 2,133 foreign establishments for which the agency could not identify a previous inspection. Agency officials told us that this count included

[21]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year. Our analysis includes all foreign and domestic inspections that were identified in FDA's data as being either related to the drug application approval process or GMP. It does not include a small number of other inspections, such as those related to problems identified by consumers or health care professionals.

registered establishments whose drugs are being imported into the United States that have never been inspected but also included other types of establishments, such as those whose products were never imported into the United States or those who have stopped importing drugs into the United States without notifying FDA. FDA was unable to provide us with counts of how many establishments fall into each of these subcategories. Of the remaining 1,116 establishments on FDA's list, 242 had received at least one inspection, but had not received a GMP surveillance inspection since fiscal year 2000,[22] and the remaining 874 establishments had received at least one GMP inspection since fiscal year 2000. Of these 874 establishments, 326 had last been inspected in fiscal years 2005 or 2006, 292 were last inspected in fiscal years 2003 or 2004, and the remaining 256 received their last inspection from fiscal year 2000 through fiscal year 2002.

FDA has increased the number of foreign establishments it inspects, most of which are concentrated in a small number of countries. From fiscal year 2002 through fiscal year 2007, the number of foreign establishment inspections FDA conducted annually varied from year to year, but increased overall from 222 in fiscal year 2002 to 295 in fiscal year 2007. During this period, FDA inspected establishments in a total of 51 countries. More than three quarters of the 1,445 foreign inspections the agency conducted during this period were of establishments in ten countries, as shown in table 2. The country with the most inspections during this period was India, which had 200 inspections. Inspections of establishments located in India increased from 11 in fiscal year 2002 to 65 in fiscal year 2007.

[22]According to FDA officials, some of these establishments may have received an inspection for another type of product, such as a veterinary drug.

Table 2: Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the U.S. Mark t, by Country f r the 10 Most Frequently Inspected Countries, Fiscal Year 2002 through Fiscal Year 2007

	Number of inspections							
Country	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007[a]	Total	Number f establishments[b]
India	11	19	38	33	34	65	200	410
Germany	24	15	35	25	19	22	140	199
Italy	17	30	26	21	18	19	131	150
Canada	29	12	17	23	23	19	123	288
United Kingdom	19	22	15	18	15	13	102	169
France	14	15	13	12	16	24	94	162
China	11	9	17	21	17	13	88	714
Japan	11	13	14	21	13	15	87	196
Switzerland	12	12	11	17	9	14	75	83
Ireland	11	5	11	14	3	11	55	61
All other countries	63	38	63	61	45	80	350	817
Total	**222**	**190**	**260**	**266**	**212**	**295**	**1,445**	**3,249**

Source: GAO analysis of FDA data.

[a]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

[b]This count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections.

The Need to Conduct Preapproval Inspections Associated with NDAs and ANDAs Drives FDA's Selection of Foreign Establishments

While enforcing GMP compliance through surveillance inspections is FDA's most comprehensive program for monitoring the quality of marketed drugs, FDA's inspections of most foreign establishments occur as part of the agency's review of an NDA or ANDA. Agency officials said that FDA may need to inspect establishments involved in the manufacture of the drug referenced in an NDA or ANDA in order to meet specific goals for the timely review of these applications. As we reported in 1998 and we still found in 2007, most inspections of foreign manufacturers occur only when they are listed in an NDA or ANDA. For fiscal years 2002 through 2007, 88 percent of FDA's inspections of foreign establishments were conducted as part of the preapproval process. When FDA receives an NDA or ANDA, CDER officials review the inspection history of each establishment listed on the application. According to FDA officials, if an establishment listed on the NDA or ANDA has received a satisfactory GMP inspection in the previous 2 years and the agency has no new concerns,

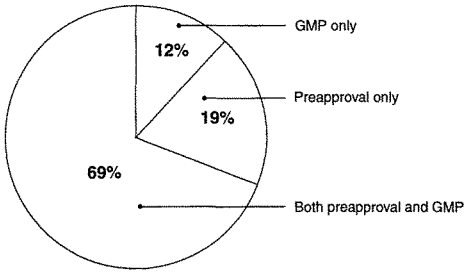
FDA will consider this inspection sufficient and will not perform a preapproval inspection of this establishment.[23]

FDA often includes a GMP inspection when it visits an establishment for a preapproval inspection. As presented in figure 2, from fiscal year 2002 through fiscal year 2007, the majority of FDA's foreign inspections combined a preapproval inspection with a GMP inspection. According to FDA officials, because foreign establishments are inspected infrequently, it is expedient for investigators and laboratory analysts to conduct preapproval inspections and GMP inspections during the same visit to a foreign establishment. During one establishment visit, FDA investigators can conduct inspections related to multiple compliance programs.[24] Because a GMP surveillance inspection examines the major manufacturing systems at an establishment, the results of such an inspection can be generalized to all products manufactured at a particular establishment. FDA can thus use the results of the combined inspection to make decisions in the future if that establishment is listed again in another NDA or ANDA.

[23]According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product.

[24]Compliance programs outline procedures for conducting different types of inspections, including preapproval inspections for drugs that are the subject of an NDA or ANDA, drug manufacturing inspections, and drug repacker and relabeler inspections.

Figure 2: FDA Foreign Establishment Inspections by Type of Inspection, Fiscal Y ar 2002 through Fiscal Year 2007

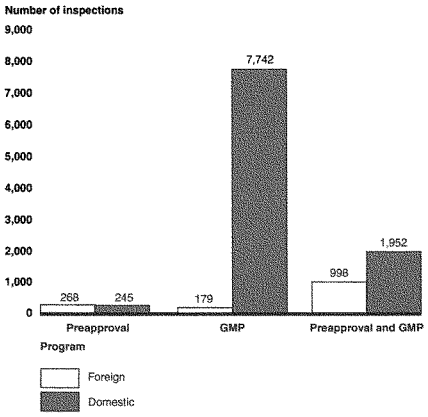


Source. GAO analysis of FDA data

Note: Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA conducts fewer GMP surveillance inspections of foreign establishments than it does of domestic ones. Of the 1,445 foreign establishment inspections conducted from fiscal year 2002 through fiscal year 2007, 1,177 inspections included a GMP component, of which 998 were conducted in conjunction with a preapproval inspection. In contrast, FDA conducted 9,694 domestic establishment inspections that included a GMP component, of which 7,742 were not conducted in conjunction with a preapproval inspection. Figure 3 shows a comparison of foreign and domestic inspections, by type of inspection.

Figure 3: Number of FDA Foreign and Domestic Establishment Inspecti ns, by Type of Inspection, Fiscal Year 2002 through Fiscal Year 2007



Source GAO analysis of FDA data

Note: Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA's funding for its domestic and foreign inspection programs is consistent with this approach. From fiscal year 2002 through fiscal year 2007, FDA dedicated more funding to domestic establishment inspections than foreign establishment inspections. The agency dedicated more funding to conduct foreign preapproval inspections than foreign GMP surveillance inspections, as shown in table 3.

Table 3: FDA Funding for Foreign and Domestic Inspections Related to Human Drugs, Fiscal Year 2002 through Fiscal Y ar 2007

Activity (dollars in thousands)	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007[a]
For ign						
Preapproval inspections	$8,274	$8,515	$8,406	$8,604	$7,544	$7,558
Postapproval inspections	5,256	5,177	5,150	5,224	5,261	5,191
Domestic						
Preapproval inspections	21,846	23,008	23,965	25,213	21,775	23,532
Postapproval inspections	23,102	28,601	27,989	28,270	27,607	28,452

Source: GAO analysis of FDA data.

[a]Fiscal year 2007 funding is estimated.

FDA's Risk-Based Process Is Used to Select Relatively Few Foreign Establishments for GMP Surveillance Inspections

Relatively few foreign establishments identified through CDER's risk-based site selection process are selected for GMP surveillance inspections. In fiscal year 2007, after using this process to rank the 3,249 establishments by their potential risk level, CDER forwarded to ORA a list of 104 foreign establishments that it considered to be a high priority for inspection. Of these, CDER requested that ORA complete GMP surveillance inspections of 25 establishments and FDA officials estimated that about 30 such inspections were actually completed in fiscal year 2007. In fiscal year 2008, CDER submitted a list of 110 foreign establishments to ORA, with a negotiated target of at least 50 inspections.

The application of the risk-based site selection process does not ensure that the foreign establishments posing the greatest potential risk are selected for GMP surveillance inspections. First, FDA officials acknowledge that they do not have an accurate list of foreign establishments manufacturing drugs for the U.S. market to use in the application of the risk-based process. Second, the usefulness of the risk-based process is weakened by the incomplete and possibly inaccurate information on those foreign establishments that FDA has not inspected recently, as well as those that have never been the subject of a GMP surveillance inspection. As a consequence, FDA lacks sufficient data to make an accurate assessment of the potential risk of such establishments. FDA recognized the effect of such data limitations on the domestic application of the risk-based process and undertook a data quality improvement initiative in fiscal year 2005, but it has yet to make a comparable effort to improve its data on foreign establishments.

To help account for the differences in information available to FDA between foreign establishments that have and have not been inspected, the agency categorizes establishments into one of three groups for the purposes of examining risk scores: (1) those that have received a GMP surveillance inspection since fiscal year 2000; (2) those that have not received a GMP surveillance inspection since fiscal year 2000, but have received another type of inspection in that time (for example, a preapproval inspection or a veterinary drugs inspection); and (3) those that may never have received an inspection.[25] These groups were created to account for limitations in the data and are not designed to indicate relative risk among groups. FDA officials told us that risk scores can be more readily compared within a group, than among groups. In 2007, FDA selected 33 establishments from the first group, 31 from the second group, and 40 from the third group to create the list of 104 establishments it submitted to ORA.

FDA officials indicated that they do not know if the establishments on the prioritized list forwarded to ORA differ significantly from each other in risk level. Consequently, they do not necessarily select the highest ranked establishments and therefore consider the locations of other planned inspections in making a final determination of foreign establishments from the prioritized list for GMP surveillance inspections. According to FDA officials, this gives them needed flexibility to make selections that will make efficient use of available resources. For example, if ORA is sending an investigator and laboratory analyst to a particular region in China for a preapproval inspection and an establishment in the same region appears on the prioritized list for GMP surveillance inspections, ORA might add this establishment to the inspection itinerary.

[25]This third group may include registered establishments whose drugs are imported into the United States. However, some establishments in this group may have received an inspection under a different FEI number, be shippers rather than manufacturers, only manufacture products other than human drugs, or never have or no longer have their drugs imported. FDA was unable to provide counts of how many establishments fall into each of these subcategories.

Challenges Unique to Foreign Inspections Influence the Manner in Which FDA Conducts Such Inspections

Inspections of foreign drug establishments pose unique challenges to FDA—in both human resources and logistics. For example, unlike domestic inspections, FDA does not have a dedicated staff devoted to conducting foreign inspections and relies on volunteers. In addition, unlike domestic GMP surveillance inspections, foreign establishment GMP surveillance inspections are announced in advance and inspections cannot be easily extended due to travel itineraries that involve more than one establishment. Other factors, such as language barriers, can also add complexity to the challenge of completing foreign establishment inspections.

According to FDA officials, the agency does not have a dedicated staff to conduct foreign inspections. They explained that the same investigators and laboratory analysts are responsible for conducting both foreign and domestic inspections. These staff members must meet certain criteria in terms of their experience and training to conduct inspections of foreign establishments. For example, they are required to take certain training courses and have at least 3 years of experience conducting domestic inspections before they can be considered to conduct a foreign inspection. FDA reported that it currently has approximately 335 employees who are qualified to conduct foreign inspections of drug manufacturers. Approximately 250 of these employees are investigators and 85 are laboratory analysts. These counts do not represent the number of individuals that actually conduct foreign inspections in a given year. Not all investigators and laboratory analysts who are qualified to conduct a foreign inspection do so in a given year, while others may perform multiple inspections during the same period. Using data from FACTS, we found that the total number of employees conducting pre-approval and GMP surveillance inspections of drug manufacturing establishments, either foreign or domestic, decreased from 587 in fiscal year 2002 to 446 in fiscal year 2007, as shown in table 4. However, of these, the number of employees who conducted foreign inspections of drug manufacturers increased from 100 to 141 during that same period. While an investigator and analyst team may participate in foreign inspections, FDA officials stated that in certain circumstances, such as inspections that do not involve the review of laboratory facilities, only an investigator is sent.

Tabl 4: Number of FDA Employees Conducting Inspections, Fiscal Year 2002 through Fiscal Year 2007

Locati n f inspection	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007[a]
Employees who conducted foreign inspections	100	94	117	114	102	141
Employees who conducted foreign or domestic inspections	587	595	539	512	478	446

Source GAO analysis of FDA data.

[a]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA relies on investigators and laboratory analysts to volunteer to conduct foreign inspections. FDA officials told us that it is difficult to recruit investigators and laboratory analysts to voluntarily travel to certain countries. However, officials noted that the agency provides various incentives to recruit employees for foreign inspection assignments. For example, employees receive a $300 bonus for each three week trip completed. FDA indicated that if the agency could not find an individual to volunteer for a foreign inspection trip, it would mandate the travel. However, FDA does not typically send investigators and laboratory analysts to countries for which the U.S. Department of State has issued a travel warning nor would it mandate travel to such a country.[26] We found that 49 foreign establishments registered as manufacturers of drugs for the U.S. market were located in 10 countries that had travel warnings posted as of October 2007.[27] However, FDA officials told us that in the past they have conducted inspections in countries with travel warnings. They also provided us with one example in which an establishment in a country with a travel warning hired security through the U.S. Department of State to protect the inspection team.

FDA also faces several logistical challenges in conducting inspections of foreign drug manufacturing establishments. FDA guidance states that inspections at foreign facilities are to be approached in the same manner as domestic inspections. However, the guidance notes that one main difference posing a significant challenge to the inspection team abroad is the logistics borne by the program itself. For example, FDA is unable to conduct unannounced inspections of foreign drug manufacturers, as it sometimes does with domestic manufacturers. FDA policy states that the

[26]Travel warnings are issued when the U.S. Department of State recommends that Americans avoid travel to a certain country.

[27]These ten countries are Colombia, the Democratic Republic of the Congo, Haiti, Indonesia, Israel, Kenya, Nigeria, Pakistan, the Philippines, and Saudi Arabia.

agency, with few exceptions, initiates inspections of establishments without prior notification to the specific establishment or its management so that the inspection team can observe the establishment under conditions that represent normal day-to-day activities.[28] However, prior notification is routinely provided to foreign establishments. FDA recognizes that the time and expense associated with foreign travel requires them to ensure that the foreign establishment's managers are available and that the production line being inspected is operational during the inspection. In addition, FDA does not have explicit authority to inspect establishments in foreign countries, and it therefore may have to obtain permission from the government and company prior to the inspection. FDA officials explained that, in some cases, investigators and laboratory analysts may need to obtain a visa or letters of invitation to enter the country in which the establishment is located. In addition, FDA does not have the same flexibility to extend the length of foreign inspection trips if problems are encountered as it does with domestic inspections because of the need to maintain the inspection schedule, which FDA officials told us typically involves inspections of multiple establishments in the same country.

FDA officials also told us that language barriers can make foreign inspections more difficult to conduct than domestic inspections. The agency does not generally provide translators in foreign countries, nor does it require that foreign establishments provide independent interpreters. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, who may not be a translator by training, rather than rely on an independent translator.

Concluding Observations

Millions of Americans depend on the safety and effectiveness of the drugs they take. More than nine years ago we reported that FDA needed to make improvements in its foreign drug inspection program. Yet, our preliminary work indicates that fundamental flaws that we identified in the management of this program in 1998, continue to persist. FDA still does not have a reliable list of foreign establishments that are subject to inspection. As more imported drugs enter the United States, it becomes increasingly important that foreign establishments receive appropriate

[28]ORA Field Management Directive No. 112A, Prior Notification to FDA Regulated Industries of Impending Inspections, August 1996. However, for both domestic and foreign preapproval inspections, FDA provides prior notification to the establishment.

scrutiny. We understand that FDA currently cannot inspect all foreign establishments every few years. We also recognize that FDA has taken steps to improve its management of the foreign drug inspection program by enhancing the risk-based process it uses to select establishments for GMP surveillance inspections. In addition, FDA is pursuing an initiative that is intended to improve its identification of foreign drug establishments. However, until FDA responds to systemic weaknesses in the management of this important program, it cannot provide the needed assurance that the drug supply reaching our citizens is appropriately scrutinized, and safe.

Mr. Chairman, this completes my prepared statement, I would be happy to respond to any questions you or the other Members of the subcommittee may have at this time.

Contacts and Acknowledgments

For further information about this testimony, please contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. Geraldine Redican-Bigott, Assistant Director; Katherine Clark; Robert Copeland; William Hadley; Cathleen Hamann; Julian Klazkin; Romonda McKinney; Lisa Motley; and Suzanne Worth made key contributions to this testimony.

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DRUG SAFETY: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

Testimony Before the
Subcommittee on Oversight and Investigations,
Committee on Energy and Commerce,
House of Representatives

Statement of Marcia Crosse, Director, Health Care

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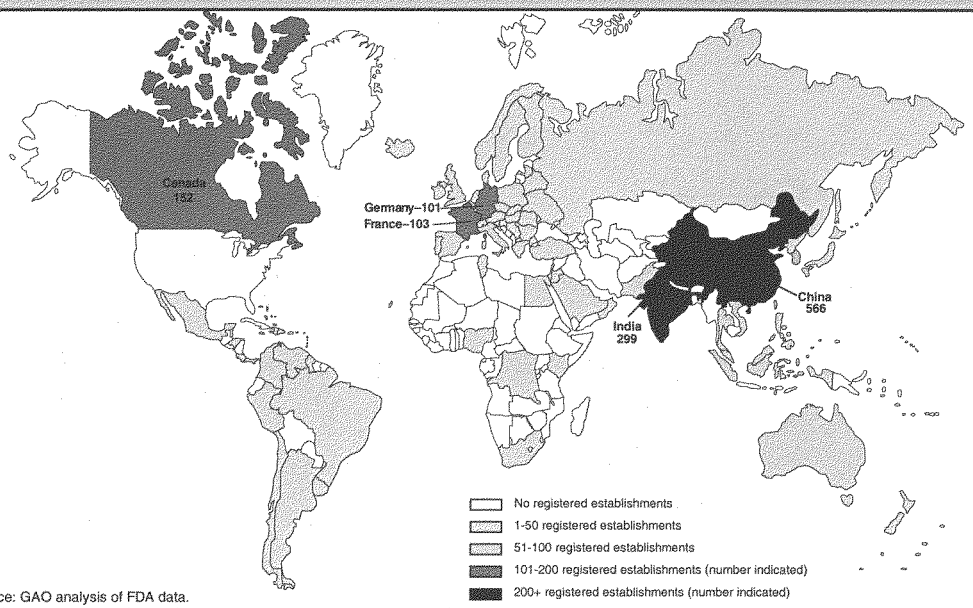
Foreign Establishments Registered to Manufacture Drugs for the U.S. Market, by Country, Fiscal Year 2007



Source: GAO analysis of FDA data.

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FDA Data Used to Estimate the Number of Foreign Establishments Subject to Inspection

Drug Registration and Listing System (DRLS):

- Contains information on about **3,000** foreign establishments registered to manufacture drugs for the United States.
- FDA does not routinely verify the information provided by establishments.

Operational and Administrative System for Import Support (OASIS):

- Contains information showing that about **6,800** foreign establishments had drugs imported into the United States.
- OASIS may artificially inflate the number of foreign establishments.

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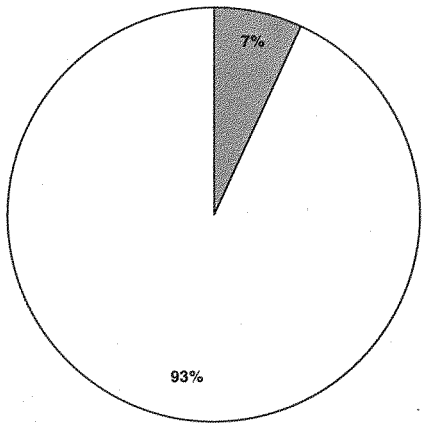
Estimated Percentage of Foreign Establishments Inspected Each Year



Source: GAO analysis of FDA data.

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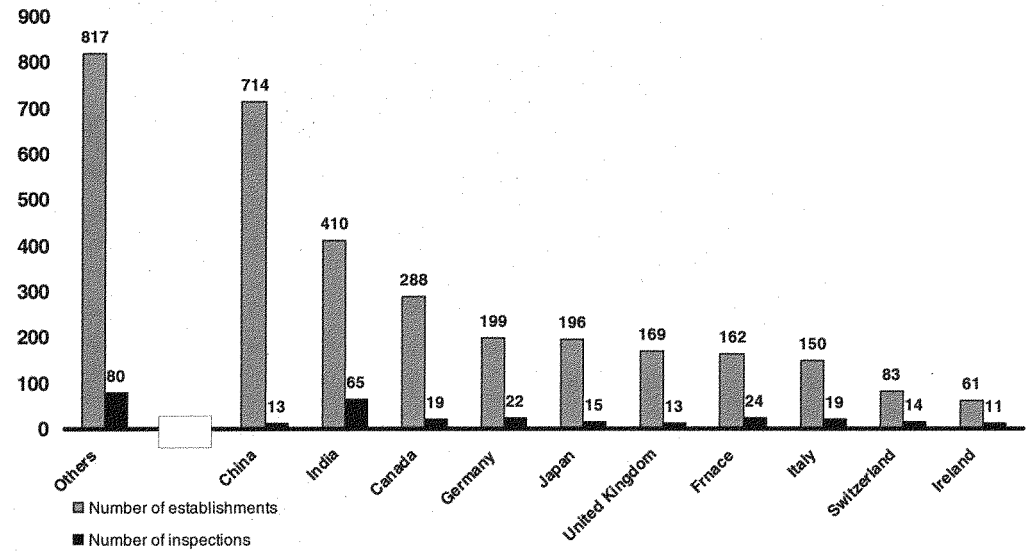
Number of Foreign Establishments and FDA Inspections for the 10 Most Frequently Inspected Countries, Fiscal Year 2007



Source: GAO analysis of FDA data.

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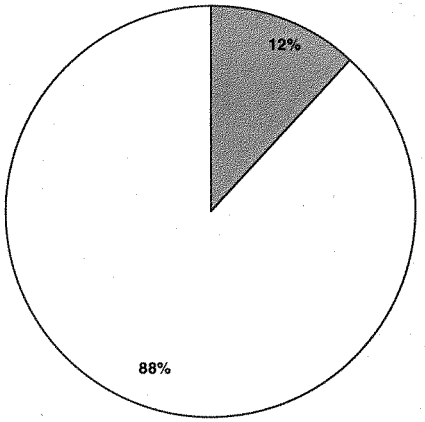
Foreign Preapproval and Routine Surveillance Inspections, Fiscal Years 2002—2007

Foreign Inspections



Source: GAO analysis of FDA data.

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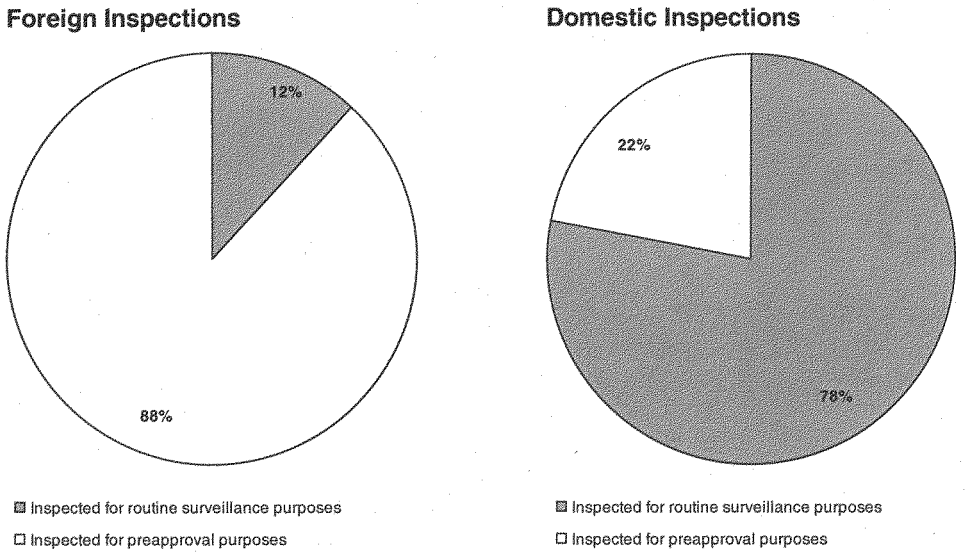
Foreign and Domestic Preapproval and Routine Surveillance Inspections, Fiscal Years 2002—2007



Source: GAO analysis of FDA data.

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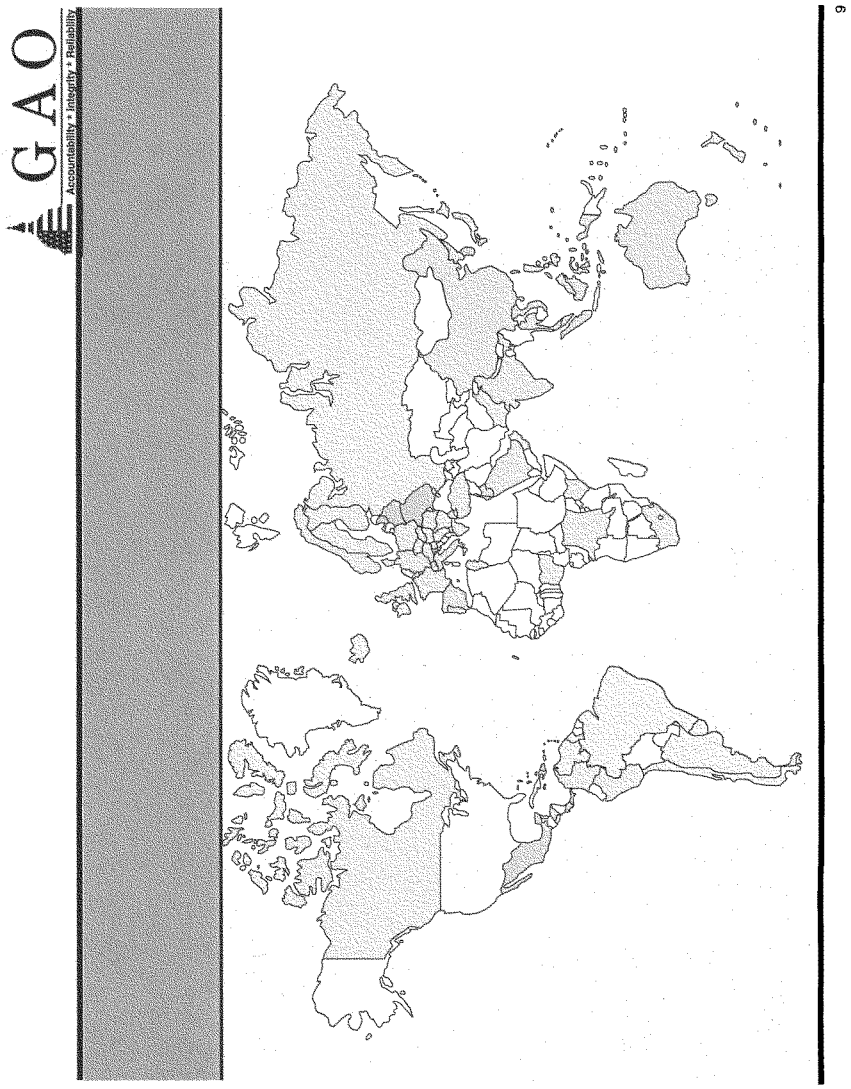
Circumstances Unique to Foreign Inspections

FDA asks staff to volunteer for foreign inspections

Arrival at facility cannot be unannounced

Lack of flexibility to easily extend inspection

Language barriers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Mr. STUPAK. Thank you, Dr. Crosse. And, Mr. Nielsen, for an opening statement, please, sir. Pull your mike up there a little closer and the green light should be on, hopefully. Thank you.

TESTIMONY OF CARL R. NIELSEN, DIRECTOR (RETIRED), DIVISION OF IMPORT OPERATIONS, OFFICE OF REGULATORY AFFAIRS, FOOD AND DRUG ADMINISTRATION

Mr. NIELSEN. Mr. Chairman, members of the subcommittee. We are to provide information to enable you to better assess the adequacy of the current FDA foreign inspection program and to help you formulate practical, effective solutions for improvement. It is unavoidable for us to also discuss FDA's import operations, since obviously foreign-made goods gained entry into the U.S. market through FDA's import procedures.

FDA manages the importation of drugs using the same entry reviewers, the same organizational structure, and the same information technology infrastructure as those used to oversee the importation of foods, medical devices, biologics, and all other regulated commodities. I recall an interview with the Journal of Commerce not long after that fateful 9/11 day. I was Director of FDA's ORA Division of Import Operations and Policy at the time. During the interview I was asked whether there were significant vulnerabilities in the current FDA import operation. I say to you today what I said then. Do the math. The import system was broken then, and it is even more so now. The volume of lines of entry have more than tripled since 1999, while resources have remained essentially static or have been reduced.

So, is FDA's foreign drug inspection program adequate to prevent entry of unsafe drug products? Let us do a quick review of some relevant information. Maybe some simple arithmetic can help us come to a logical conclusion. First, FDA is expected to handle approximately 18 million lines of entry for all regulated commodities this year. Drugs and biologics comprise approximately 10 percent, or 1.8 million lines, foods and cosmetics comprise approximately 60 percent, and medical devices comprise approximately 30 percent, or 5.4 million lines of entry. Number two, entries of FDA-regulated goods enter through 250 or more U.S. Customs Ports of Entry. Nationwide, there is approximately 200 field investigators and inspectors who spend most, but not all, of their time reviewing entries, collecting samples, examining cargo, and conducting investigations and inspections for all imported commodities. That is less than one person per port on average, and 90,000 entries per person on average.

There is an estimated 300,000 plus foreign manufacturers of FDA-regulated commodities. FDA conducts 500 to 900 foreign inspections per year for all industries. That is an inspection cycle of 333 to 600 years on average for all commodities. The foreign-made products are received from 200 plus countries, not just a handful of concern. FDA inspects an average 200 to 300 foreign inspectors of Rx drugs per year. Inspection of foreign manufacturers of OTC drugs are virtually non-existent. There is an estimated 3,000 to 6,800 foreign manufacturers of Rx drugs, on top of which there are thousands of OTC manufacturers. The estimated foreign inspection

cycle for the Rx industry ranges from 10 to 30 years or more, while the cycle for OTC drugs could be 50 years or more, or almost never.

Conclusion—FDA knows very little about the actual conditions of manufacture of most imported drugs, and that should be found totally unacceptable in a professed risk-based approach. Many potential risks are mitigated when good manufacturing practices are used, and many potential risks are increased when good manufacturing practices are not used. In order to ensure a safe drug supply, FDA needs to verify compliance by the foreign drug industry with current good manufacturing practice requirements. FDA needs to revamp its entire organizational structure and approach to managing products from the international market. There is no cheap fix. That is part of the price of a global economy. Agency oversight must follow the regulated industry to be effective.

The current, domestic-oriented organization has had decades to get this right. It has not, and I don't think it can. We are sitting here talking about the very same issues from more than a decade ago. Unless there is significant investment in the IT systems and establishment of a new organization that can implement an effective risk-management system for all imported regulated products, not just for foods and drugs, then I suspect folks will gather here in another 10 years wondering why something wasn't done this time around that could have avoided many injuries and deaths from unsafe, imported drug products.

I appreciate the opportunity to appear before you all, and I will do everything I can to avoid coming back in another 10 years on the same topic. I look forward to participating in this hearing.

[The prepared statement of Mr. Nielsen follows:]

Statement of

Carl R. Nielsen

FDA- retired, former Director of ORA's Division of Import Operations and Policy

Before the

SUBCOMMITTEE ON OVERSIGHT & INVESTIGATIONS

COMMITTEE ON ENERGY & COMMERCE

U.S. HOUSE OF REPRESENTATIVES

November 1, 2007

A. Introduction:

Mr. Chairman, members of the Subcommittee on Oversight and Investigations, I thank you for this opportunity to discuss the status of FDA's oversight of the foreign-based pharmaceutical manufacturing industry and related drug products. I retired from FDA in February 2005 after 32 years of government service, 28 of which I served in the U.S. Food and Drug Administration, Office of Regulatory Affairs (ORA). Besides serving as a senior special agent with FDA's ORA/Office of Criminal Investigations, I served in capacities as a consumer safety officer carrying out duties as a field investigator, a resident-in-charge, a field compliance officer, a first line supervisor of a field unit dedicated to import operations, lead compliance officer with the original Team Biologics Core Team based in ORA headquarters, and, finally, for nearly six years, I served as Director of ORA's Division of Import Operations and Policy (DIOP). Since my retirement I have been self-employed as a regulatory consultant as C. Nielsen Consulting and am co-founder of FDAImports.com.

I understand it is the purpose of this Subcommittee's hearing to evaluate FDA's ability to oversee the foreign drug industry to ensure public health and safety. The short answer – the current paradigm is grossly inadequate, is held together by bailing wire, and is incapable of determining or verifying the safety and efficacy of most imported drug products. Product liability is protecting us more than FDA's oversight of the international supply of pharmaceuticals. Not only are financial and human resources woefully inadequate, the current FDA organization is not designed and funded to adequately oversee the foreign industry, to effectively manage and administer the related programs, and to ensure the delivery of safe and effective imported drug products into the United States through secure supply chains.

B. Importance of Surveillance Drug Manufacturer Inspections

The traditional first and internationally recognized primary method for the agency to ensure drug products are safe and effective after product approval is to conduct current good manufacturing practice (cGMP) inspections to ensure the firms are in compliance with requirements of the current good manufacturing practice regulations (cGMPRs) and conditions promised in the drug applications. Drugs emerging from cGMP compliant firms means they were made in adequate facilities using appropriate systems and practices are in place to ensure the safety and effectiveness of each batch of finished drug. cGMP compliant firms have systems in place to ensure incoming components including ingredients meet quality specifications.

Prescription (Rx) drug manufacturers are required to identify their sources of ingredients, including Active Pharmaceutical Ingredients (API's), used to make their finished drugs are the same ones identified in their drug applications. The applicants must also submit information describing product specifications and manufacturing methods for the API's. This is usually done through the Drug Master File (DMF) process in which the API manufacturer submits the information to the Agency. Today, most API's are made by foreign manufacturers.

The finished Rx drug manufacturer must also demonstrate the ingredients they use in the manufacturing process consistently produces finished products that meet all relevant specifications. Part of establishing a stable manufacturing process is ensuring the ingredients going into the process meet specifications and are of adequate purity and quality. In other words, the manufacturer of the finished drug essentially performs pilot manufacturing using the API from a specific source to make sure the finished drug meets final specifications described in the application. Use of API's from sources other than those identified in the approved drug application can result in a finished product that will not do what it is supposed to do.

During counterfeit imported API investigations in the early 1990s, we found an instance, for example, in which a patient died because a finished carbamezapine drug, an anti-convulsant, which was made with an imported counterfeit carbamezapine API, did not work. Other patients who experienced seizures using the same product became seizure free once they used another carbamezapine product. The counterfeit carbamezapine API

met identification and potency testing requirements. The investigation determined the crystalline structure of the counterfeit altered the compression characteristics of the tablet which had an adverse effect on dissolution characteristics. Consequently, the tablet did not dissolve and the carbamezapine was not delivered to the target organ to manage the seizure disorder. It apparently just passed through the intestinal tract.

Finished product testing alone is inadequate to ensure a batch of product is safe and effective. Finished product testing does have value in determining expiration dating, monitoring manufacturing processes, establishing baselines for impurity profiles and other analyses useful to identify and verify important product characteristics. But testing alone can not put the quality and safety into the product. It is the manufacturing processes and application of effective quality assurance programs that determine the quality and safety. An adequate correction for a failed product that is detected or confirmed by testing is not to just do more testing. Rather, it is to identify the cause of the failure and to implement corrective steps in the manufacturing processes to best ensure the same failures are not repeated. It is the well designed, stable manufacturing process that ensures product safety and effectiveness from one pill to the next, from one vial to the next, and one bottle to the next.

C. FDA Organizational Weaknesses Undermine Effective cGMP Compliance Programs

It is primarily FDA's Office of Regulatory Affairs' (ORA's) job to ensure the drug industry is complying with cGMP requirements by conducting inspections of the physical

plant, processes and materials. However, ORA is not directly funded to maintain baseline infrastructure to ensure appropriate inspection coverage of regulated industry. Resources are negotiated between ORA and the Center for Drug Evaluation and Research (CDER) through an annual, on-going, ORA work planning process that determines which and how many field activities will be supported for a fiscal year. These activities include domestic and foreign inspections and border operations.

The number of activities the agency plans for the year is based on the number of activities that can be accomplished by FTEs (Full-time Equivalents). The number of FTE's, though, do not directly translate to the number of warm bodies performing the activities such as inspections and entry review. In my six years as Director of the Division of Import Operations and Policy, no one could provide me a roster of personnel assigned to import duties fulltime, nor was I able to develop one. In a September 24, 1998, statement Mr. William B. Schultz, then FDA's Deputy Commissioner for Policy, stated before the Permanent Subcommittee on Investigations of the Senate's Committee on Government Affairs, " In 1992, we received approximately 1.1 million line items of imported foods and had 631 supported Full Time Equivalent employees (FTEs) to look at those items. By 1997, our line items more than doubled to approximately 2.7 million but budget limitations caused us to cut our supported FTEs to 565. Of these 565 FTEs, only 314 are what we refer to as "operational," with 112 actual investigators and 202 analyzing samples in the laboratories. (The others are support staff, including those at headquarters.)". This statement was provided in the context of describing FDA's oversight of imported foods.

From Mr. Schultz's statement one can readily see FTE's do not directly relate to the number of inspectors with feet on the ground. Out of the referenced 565 FTE's, there were 112 investigators (inspectors) to conduct entry reviews, collect samples, and examine cargo. About 1/5 of the FTE number translated to actual investigators (inspectors). FDA's FTE model means more than half the resources are spent on non-descript support staff who do not report time into the tracking systems that keep count of FDA's activities, e.g., entry review, domestic and foreign inspections, investigations, sample collections, examinations, laboratory analyses, etc. The math behind this FTE resource model is very questionable. The FTE appears to be little more than time accounting. However, only the activities of the field inspectors, investigators and laboratory analysts are accountable and only they report their time into the systems used to create the FTE model. The ORA work planning process and organizational structure need a major overhaul.

D. Disparity in FDA Inspections of Domestic vs. Foreign Drug Manufacturers

The statute requires FDA to inspect the domestic drug manufacturers every two (2) years. Historically, FDA does pretty well meeting this 2 year obligation with its scant resources. However, the industry trend for more than a decade has been to move drug manufacturing for finished drugs and API's off-shore. Unfortunately, without the external pressure on the agency, the current FDA organization has not re-deployed, and

will not re-deploy significant resources away from the domestic industry to the international arena commensurate with this industry trend.

The current FDA organizational structure and administrative processes are entrenched in overseeing the domestic industry while largely ignoring the foreign industry. Very few foreign surveillance inspections are conducted annually, and most are conducted in a very short-time frame of 2-3 days in order to save money and to get the greatest number of inspection numbers accomplished on a foreign trip. Regardless of the outcome or scope of the foreign inspections, the agency uses the number of completed foreign inspections to argue it is providing adequate coverage of the foreign industry using the least amount of resources. FDA still uses the number of completed inspections and other activities, the work widgets, to measure performance instead of the outcome of the widgets. If FDA plans 700 foreign inspections per year, for example, and the 700 foreign inspections are completed in that year, then FDA considers the planning a success. If 701 or more inspections are conducted then the work obligations and performance goals have been exceeded and performance awards may even increase.

Certainly fiscal constraints to some extent have tied the agency's hands adding to its inability to adequately oversee the foreign industry. But why would management continue to spend the same resources on the domestic industry when it is known at least the same number, or more, of the manufacturing firms are located overseas? It doesn't make sense. Certainly it is logical to expect greater risks will arise from drug industries in countries that do not have the same or similar oversight regulatory capabilities as the

United States. Simple infrastructure issues such as potable water, power supply, personal hygiene of employees and air quality can be very significant for producing products of high quality and safety. Yet, FDA's focus on domestic manufacturing – to the exclusion of foreign inspections – persists.

There is an FDA culture of not wanting to know there may be more regulatory problems outside the traditional domestic industry because the agency is already strapped with domestic regulatory issues. This "know no evil" culture enables FDA to say that no one has identified a specific risk, thus, there must be no risk – thus there is no cause for FDA action. A real comprehensive risk management approach does not just pick a subset of the universe and ignore the rest. Instead, the agency should put more value into knowing the compliance status of the entire foreign industry as thoroughly as it pursues the compliance of the domestic industry. If the agency knew the compliance status of the universe of foreign manufacturers, it would be able to develop appropriate strategies to better ensure only safe imported drugs are allowed entry into the United States. The agency would be able to direct resources to particular firms or countries or regions to facilitate compliance with U.S. requirements or prohibit access to the U.S. market.

Compliance by the foreign industry with cGMP requirements will reduce the potential risks to drug product safety and efficacy. And, a rare 2-3 day foreign inspection by itself will not adequately assess compliance with cGMP requirements. FDA's persistence of focusing resources on the inspection of the domestic industry and PDUFA pre-approval inspections, creates greater opportunity for the foreign industry to cut corners with cGMP

and other requirements without detection by FDA. The lack of credible FDA inspection presence in the foreign industry can make unbearable the temptation to reduce costs by taking short-cuts in proper cGMP controls because the likelihood of being caught is quite remote. It can become a very dangerous race and slippery slope to the lowest competitive drug price if there is no robust FDA oversight of manufacturing conditions for both domestic and foreign industries. Further, there must be a robust, risk-based border operation that integrates all relevant information including cGMP compliance as criteria for admissibility. Current FDA border operations will not, can not, readily detect shortcomings in manufacturing conditions that could cause the imported products to be unsafe. The integration of foreign inspection data with FDA's import operations requires significant resources to develop Information Technologies (IT) platforms capable of taking in, managing, evaluating, and delivering relevant information to create an effective border operation.

E. Unfair Competitive Advantages in the Foreign Industry

The lack of credible FDA inspection presence in foreign industry also creates an unfair competitive advantage for the foreign industry. The domestic industry is accustomed to experiencing an FDA inspection of 2-3 weeks duration when significant, or questionable practices are discovered. This is in stark contrast to the routine 2-3 days FDA spends inside a foreign manufacturer, regardless of inspectional findings. Obviously, the scope and detail of the 2-3 day foreign inspections are dramatically reduced, as well as FDA's ability to conduct a comprehensive assessment of the manufacturer's cGMP compliance.

One should expect the results of domestic inspections to show a greater rate of compliance with FDA requirements by U.S based firms when compared to the foreign industry, unless the brief foreign inspections are just too shallow to uncover significant cGMP issues.

Unlike the domestic industry, the foreign industry is given extensive opportunities to micromanage and influence FDA inspections. The current foreign inspection process puts the manufacturer in almost a totalitarian position to control the inspection from the time an investigator lands to the time of departure. Generally, the domestic industry is subject to unannounced inspections under FDA's statutory authority. Meanwhile, the foreign industry receives several weeks' advance notice of FDA's intent to inspect. This interlude provides foreign industry an opportunity to prepare and put on the best face for the FDA inspector knowing the inspection will likely be of a specific duration and knowing the likelihood of a timely re-inspection is remote. The FDA investigator generally is at the mercy of the foreign firm for logistic support including land transportation, food, translation of records and oral statements, and a work station other than a motel room. In essence the FDA foreign inspector or inspection team is on its own in a foreign land and is expected to be a self-sufficient traveling station with a laptop and portable printer, and maybe a government issued cell phone as a tether to Agency support on U.S. shores.

F. <u>These Weakness are not Isolated to Prescription Drugs</u>

Weaknesses in FDA's current regulatory paradigm to ensure safety of imported goods are consistent across all imported regulated goods. This includes oversight of imported pharmaceuticals, Rx and OTC alike. FDA's current import program is the primary means of overseeing the products actually arriving from foreign sources. The current import paradigm primarily focuses mostly on sampling at the border and the review of information contained in an invoice. Except for information in a few Import Alerts, the FDA decision to allow the importation of a drug shipment is not based on information related to the conditions of manufacture that can effect product safety. Even though there are a few data points beyond invoice information that are reviewed during the entry review process, information related to the current status of cGMP compliance is not one of the criteria for admissibility. ORA entry reviewers have access to the text information in multiple CDER and ORA databases, but they still do not know the current condition of manufacturing for most drugs. Few commercial shipments are physically examined outside of operations at international mail facilities and courier hubs. Shipments of less than $2000 value are essentially given a free pass as an informal Customs entry.

The ORA entry reviewers check technical requirements such as registration and listing information that have little to do with product safety, and are certainly not linked to evidence of compliance with cGMP's. Using the stove-piped databases, the reviewers try to determine whether the entry of Rx drugs, finished or API, are covered by a current drug application. Entry reviewers have to spend significant time just logging in and out of the databases in the search of information that may be related to the shipments. And even after all that time and effort, the entry reviewers still do not know what the current

manufacturing conditions are for the vast majority of the entries. It appears FDA presumes the foreign Rx drug industry complies with conditions in the approved drug applications or DMF's without a verification process.

There are similar shortcomings in the foreign inspection program for foods and drugs. For example, many of FDA's regulated foreign food processors, if inspected by FDA at the current rate, are on nearly a 200 year inspection cycle. Based on my experience and recollection, I estimate the inventory of foreign manufacturers of Rx finished drugs and API's to range from approximately 3,000 to 5,000 firms, maybe up to 6,000 firms or more. If FDA were to continue inspecting the foreign Rx industry at the historical rate of 200-300 firms per year, the manufacturers of Rx Active Pharmaceutical Ingredients (APIs) and finished drugs would be completed on an inspection cycle up to 30 years (6,000 firms divided by 200 inspections per year). Such a cycle would mean a 2-3 day inspection once every 30 years in the worst case to make sure drugs are made in a manner to ensure safety and efficacy. The best case scenario may be approximately a 10 year inspection cycle (3,000 divided by 300).

The inspection rate of foreign OTC manufacturers may range into several decades, maybe a 50 year cycle or more. As I recall, the number of foreign firms related to OTC drugs could be several thousand, maybe tens of thousands or more, above the Rx industry. Oversight of OTC drugs (finished drugs and API's) at the border is even less rigorous than that for Rx drugs. They simply are not on the radar as they are not funded in the ORA work plan. There is no requirement for the OTC industry to submit an

application that describes manufacturing processes including the source of Active Pharmaceutical Ingredients (API's) and other ingredients. The OTC finished drugs must meet monographs and labeling requirements. The monographs are basically product formulation requirements coupled with labeled uses allowed by the agency. OTC drug manufacturers are also required to comply with the same current good manufacturing regulations (cGMP's) as the Rx industry. And, failure to implement good manufacturing practices can result in unsafe and ineffective drug products. But in foreign OTC manufacturing, cGMPs are virtually never assessed.

It was reported in October 2006, that an outbreak of DEG (diethylene glycol) poisoning occurred in Panama, resulting in multiple cases of illnesses and death. The tainted product was an OTC drug. It is my understanding the DEG (diethylene glycol) found in toothpaste made in China discovered in Panama and the United States in May 2007 was not a result of product tampering of the finished product, but a result of deficient cGMP practices that failed to verify the identification and specifications of the incoming raw materials. The DEG was not related to the API, but was related to the quality of the excipient or inactive ingredient of the toothpaste. Good manufacturing practices could have prevented the incident, and robust oversight could have verified good manufacturing practices were implemented.

The OTC industry market may even have greater impact on public health and safety than the Rx industry since the exposure is so great. Most people self-medicate minor ailments using OTC products. It's the first cost-effective treatment plan for the consumer, if used

properly. However, there's even less known about the conditions of manufacture of the imported OTC products. Historically, inspection of the OTC industry has been a very low FDA priority compared to the Rx industry. While at FDA, I do not recall any discussions about conducting inspections of foreign OTC firms in any FDA work plan process. I seriously doubt any surveillance inspections have been done in recent years, if ever, unless it was connected to an Rx manufacturer or follow-up activity related to an injury or illness.

Consequently, the FDA oversight of OTC products from foreign sources are largely relegated to the current border operations, and that should not make anyone feel better. The absence of reliable information about current manufacturing conditions of most foreign manufacturers results in a lot "unknowns". This includes the release by FDA of foreign made OTC products of unknown quality and safety. There is no process to routinely identify the conditions of manufacture or compliance with requirements of the monograph before allowing entry into the U.S. market. Compliance with cGMPs by the foreign manufacturer and a risk-based border operation, similar to the one proposed in the FDA 2003 Import Strategic Plan, could have prevented incidents like the discovery of DEG in imported toothpaste.

G. Foreign Made Drugs – a Close Cousin to other Foreign Made Goods

There are an estimated 300,000 + foreign manufacturers of all FDA regulated products dispersed among 200+ foreign countries. Products enter through approximately 300 U.S.

Customs ports of entry. For years FDA has allocated less than 200 inspectors (on average of less than 1 per port) to conduct entry reviews, collect samples and conduct physical examinations and investigations of all imported products including foods and drugs. FDA typically inspects 500-900 foreign firms per year, the vast majority of which are drug or device approval driven (and funded). There are approximately 18 million lines of entry for all FDA regulated products, of which approximately 10% are drug related. About 60% of the entries are food and cosmetic related. Approximately 25-30% of the lines of entry are radiation emitting and medical devices.

Do the math. The current FDA organization, IT systems and regulatory paradigm have not, and can not effectively manage the foreign industries or mitigate the related risks. More money alone may not be enough.

Mr. STUPAK. Thank you, Mr. Nielsen. Mr. Hubbard, please, for your opening.

TESTIMONY OF WILLIAM HUBBARD, SENIOR ADVISOR, COALITION FOR A STRONGER FDA

Mr. HUBBARD. Thank you, Mr. Chairman. I have a written statement, which is remarkably similar to yours, so I won't repeat what you said, but I will say it is frustrating to be back here over and over again, as Mr. Nielsen said. I remember being here in 1986 with these issues, in the 1990s, and your hearings in 2004, and now we are back again. And it does seem to be a continuing concern. It doesn't get fixed.

But bottom line, though, is how can we live with a process in which you have this pervasive regulatory system over U.S.-produced drugs, with inspections and rigorous adherence to quality controls, but yet the majority of our drugs are coming from foreign countries and often developing countries, which rarely get inspected. I think that is an indefensible contradiction, and clearly the examples you have all given are real. Drug ingredients coming from countries like China and India that have weak process controls. Counterfeiting of drugs is endemic around the world. In some countries, you are more likely to get a counterfeit than a real drug. And, of course, Americans are going to the Internet and buying drugs that they think are coming from Canada, and in fact they are coming from some of the darkest corners of the world.

So I must say this does need to be addressed. I worked at FDA almost 30 years, with 14 acting and permanent commissioners, and all of them were forced to play this public health version of the kids' game, whack-a-mole, in which they were forced to shift resources to wherever the squeakiest wheel was of the day and try to fix that. That was all it was, and nothing ever seemed to get fixed. And so you see now, inadequate food inspections, you know, inspections of clinical trials, inspections of human tissues, and of course the drug inspections for foreign firms lags the worst in many ways.

So the safety of drug imports just keeps coming back over and again every few years, but we just don't seem to fix it. So I hope this time the committee will make a tenable effort to make this a point of concern and move to fix it. This committee has done tremendous things for the FDA over the years, and I hope that this is one that you will stay with and tackle. Thank you very much.

[The prepared statement of Mr. Hubbard follows:]

Statement By

William K. Hubbard

Coalition for a Stronger FDA

Before the

Subcommittee on Oversight and Investigations

Committee on Energy and Commerce

U.S. House of Representatives

Washington, DC

November 1, 2007

INTRODUCTION

Mr. Chairman and members of the Committee, I am William K. Hubbard. Before my retirement after 33 years of Federal service, I served for many years with the U.S. Food and Drug Administration, and for my last 14 years was an FDA Associate Commissioner responsible for, among other things, FDA's regulations and policy development. Although I remain retired since my departure from FDA in 2005, I serve as an advisor to The Coalition for a Stronger FDA, a consortium of patient, public interest, and industry organizations whose mission is to urge that FDA's appropriations be increased. The Coalition and its constituent members are greatly concerned that FDA's resource limitations have hampered the agency's ability to ensure the safety of our food and drug supply. Today's hearing is a timely example of one of those concerns—the massive increase in pharmaceuticals being imported into the United States at a time in which FDA's capacity to oversee those foreign producers is in serious doubt. Accordingly, I wish to thank the Committee for inviting me to testify on that subject today.

BACKGROUND

As you know, Congress created the current regulatory structure for assuring the safety of human drugs in 1938, through its enactment of the Food, Drug and Cosmetic Act. That statute recognized that drugs could be a key component of our health care system, but that drugs were also powerful chemicals with the capability to produce great harm if not carefully regulated. Thus Congress determined it necessary to create a relatively

pervasive regulatory system which requires that drugs be carefully tested before being approved for marketing, and produced under exacting quality control standards. Subsequent FDA regulations have provided specific requirements for drug manufacturers to meet in carrying out Congress's direction. So, today, drugs are cautiously tested, first in animals, then in humans, and approved by FDA only if their medical benefits outweigh any risks they pose. Once approved for marketing, a drug must be manufactured under specific controls mandated by FDA—known as Good Manufacturing Practices. These include requirements that active ingredients of the drug be of a prescribed purity, strength and quality; that the drug be made in well controlled, sanitary conditions; that its labeling and packaging be equally well controlled; and that laboratory tests of the drug be performed routinely using well established scientific methods and properly calibrated equipment to confirm that the drug is always produced in the form approved by the FDA.

A RECORD OF REMARKABLE SUCCESS

The result of this regime established by Congress and implemented by the FDA has been unsurpassed, and perhaps unequaled, in my opinion, by any American industry. FDA now approves new drugs as fast or faster than any other country in the world (thanks to the user fee program enacted by this Committee). The high standards for drug safety and efficacy that you and the FDA have demanded have led to a cascade of new discoveries across the decades that have placed the U.S. pharmaceutical industry far above foreign competitors in quantity and quality of new therapeutics. Indeed, countries around the world look to the FDA as the "gold standard" for determining if a new drug should be

approved and for establishing safe manufacturing controls for marketed drugs. Today, physicians, pharmacists, and their patients have a very, very high confidence that the drugs they prescribe, dispense, and use are well understood, well made, and will perform as expected.

THE GLOBAL SITUATION

The portrait of pharmaceuticals elsewhere around the world is not so positive. Drugs developed and produced in other countries do not always have the same record of therapeutic success as American pharmaceuticals. But perhaps more importantly, unlike the relatively closed U.S. drug market, in most countries these products are subject to normal arbitrage, which means that drugs move about much as do electronics, apparel, auto parts and thousands of other goods. This has meant that drugs are often purchased from suppliers who have little or no oversight by regulatory bodies; that key elements of safe drug production are ignored—such as quality testing, expiration dating, and labeling controls; and that producers of substandard and counterfeit drugs have a relatively easy access to the marketplace.

Specific examples of dangers in the international drug market abound. Let me list just a few:

- The recent substitution of ethylene glycol (antifreeze) for pharmaceutical grade glycerin in an elixir that was linked to 46 deaths in Panama, as well as to other deaths in Nigeria, India, South Africa, and Argentina. Those

cases were ominously reminiscent of a similar contamination 1996 that was associated with the deaths of 85 children in Haiti. In both cases, the sources of the substitution were reported to be Chinese drug manufacturers, as was the diethylene glycol contamination of toothpaste that was found recently in many countries, including the United States.[1]

- About 20% of drugs in the European Union are now purchased through their system of "parallel trade," meaning they can come from virtually anywhere; and in just the past 2 years, seizures alone of fake drugs in the EU went from 500,000 tablets to almost 3 million.
- A recent "sting" operation by the The Sunday Times of London set up a phony drug wholesaler, who was able to buy large quantities of counterfeit drugs from a Chinese manufacturer, who was reported to make pharmaceutical ingredients for legal sale by day and fake drugs for illicit sale by night. The Times reported that counterfeiters are increasingly turning from fake handbags and currency to drugs, because the drugs are so easy to make and sell on world markets.
- The World Health Organization has reported that in some areas of the world, particularly parts of Africa and Asia, more than one-half of the pharmaceutical supply is counterfeit. Indeed, drug counterfeiting is considered to be endemic around the world, with the United States thus far one of the few exceptions. China is alleged to be a principle world supplier of such products.

[1] Ironically, and sadly, it was diethylene glycol substitution for glycerin in an elixir that killed over 100 Americans in 1937 and led Congress to enact the Food, Drug and Cosmetic Act, and thus create the drug safety system that the United States relies upon today..

- Within China itself, the annual number of deaths from counterfeit and substandard drugs is reported to be between 200,000 and 300,000.

I could go on with numerous other examples, many of which would include a frequent reference to China. But I do not intend to suggest that "Made in China" should become a synonym for danger. That country's enormous economic development in recent years has made it the source around the world of increasing percentages of many nation's consumer goods. Here in the United States, it is estimated that 40% of all consumer products we purchase originate in China. Most are assuredly safe and an attractive bargain for Americans seeking to stretch their income as far as possible.

But drugs are not socks or running shoes. They are special, and Congress recognized their unique importance to health—and their potential risk—when it gave FDA the authority so many years ago to create a comprehensive regulatory system over pharmaceuticals. I believe FDA did its part, and did it well—by bringing to bear the best scientific knowledge of drug development and production to create rules and procedures for assuring that our drugs are safely manufactured. However, I believe that we may now be at a turning point at which our future actions will determine whether we will go the way of other countries or stay on the path that has served us so well.

IN WHAT DIRECTION ARE WE HEADED?

As the Committee has documented in hearings this year with respect to imports regulated by FDA, the United States has seen a massive change in sourcing of many foods and drugs in recent years. Today, perhaps two-thirds of our pharmaceuticals have foreign components, either as so-called "finished dosage form" -- the pill we get from the pharmacy; or Active Pharmaceutical Ingredient -- the active ingredient that is shipped to the United States for production of the final pill form. And that ratio is predicted to climb to 80% or more by the end of this decade. Yet in the face of this flood of drugs and drug ingredients from overseas, what are we doing to assure that they are as safe as drugs produced in this country? The facts are fairly dismal:

- FDA's inspection rate for imported drugs (and drugs ingredients) when they arrive at a U.S. port is around 1%, which means that the vast majority of imported drugs do not receive an FDA inspection upon entry into this country.
- The chances of an imported drug being sampled and tested at entry to this country is even lower; in fact, of the millions of drug shipments arriving from foreign countries last year, only 340 samples were taken for laboratory testing.
- Although there are approximately 3000 foreign drug manufacturers registered with the FDA, only 341 were inspected last year. And even that number is misleading, as most of those inspections were so-called "preapproval inspections" for drugs about to be approved by FDA for

marketing. The number of good manufacturing compliance inspections was perhaps two dozen or so.

- The Food, Drug and Cosmetic Act dictates that each drug manufacturer be inspected at least every two years, but the current rate of foreign inspections is infrequent at best. Please stop and think about that – we are buying ever larger percentages of our drug ingredients from producers in developing countries who receive virtually no FDA inspection, despite a statutory requirement that they be inspected regularly.
- The two biggest foreign suppliers of drug ingredients are China and India, both developing countries with weak regulatory systems over drug manufacturers; that have a track record of being the source for dangerous and substandard drugs; and in whose facilities FDA inspectors have at times found horrendous conditions.
- The information technology systems used by FDA to track registrations of foreign drug manufacturers and actual imports from those manufacturers are not linked and are so poorly coordinated that FDA inspectors often cannot tell if a firm actually importing a drug is even registered at all.

So, then, the question we must ask is where will we go as a nation, with respect to the safety of our pharmaceuticals. Will we accept the fact that drugs produced in many different countries, often in developing nations without a tradition of high standards, will be the main source for our health care and merely hope for the best? Or will we take the steps necessary to assure that these products are as safe as our scientists can make them?

THE GOOD NEWS

Unlike the circumstances with imported foods, for which the regulatory paradigm is clearly antiquated and dysfunctional, our drug regulatory system is not crying out for overhaul, for the following reasons:

1) Congress has provided FDA with a strong statutory construct for regulating the manufacturing of pharmaceuticals;

2) FDA has implemented that statute with effective, science-based regulations governing drug production;

3) Scientists within the Federal government, the pharmaceutical industry and academe have worked closely over the years to develop techniques for drug manufacturing and testing that have passed the test of time—that is, as a nation we are good at this and the rest of the world looks to us for leadership.

4) U.S. drug manufacturers accept the need for high standards in drug development and manufacturing and generally adopt those standards faithfully, including taking care to secure their chain of supply of drug ingredients.

5) Drugs made in the United States under FDA's rigorous quality control standards have an extraordinarily good safety record, as measured by the paucity of manufacturing defects and deaths and illnesses related to manufacturing deficiencies.

WHAT MUST BE FIXED

But there is one critical piece of the drug regulatory system that is broken, and must be corrected if we are to maintain our good safety record in drug production. That is the enforcement of the rules that govern drug production. It does no good to have rules if they are not obeyed, no good to set high standards if they are not used, and no good to develop advanced scientific skills if they are not employed. That countries such as China have a record of serious problems in drug manufacturing is indisputable. And the disparity in drug inspections – in which FDA inspects U.S. facilities regularly and those in China and India almost never -- is indefensible.

Some would say that we should not be buying products such as drugs from developing nations, but that flies in the face of the reality of global free trade. Others would rely upon agreements negotiated with foreign countries, under which those nations would assure the safety of drugs exported to the United States. I believe that a developing country is incapable of effectively implementing such an agreement, and that such a course of action is a prescription for frustration. In the end, I believe we must rely upon what we know has worked in the past to protect our drug supply – the FDA.

I believe FDA's scientists and regulatory officials are nothing short of terrific. They are well trained, intensely dedicated to the public health, and a true bargain for the American taxpayer. But they have been handed a task -- an expectation -- that they realistically cannot fulfill with their current resources. Simply put, they must be given two crucial things:

- Sufficient staff to do the work. FDA must have the people to examine and sample more imported drugs at the border, to dispatch inspectors to the facilities in other countries making these drugs, and to develop modern risk assessment techniques for gauging where and when to look for drug safety problems; and

- Funds for information technology. The agency's IT systems are woefully outdated, yet could make the oversight of imported drugs far more effective with a relatively small investment in funding. The IT systems should be configured in a way that allows the agency to use a myriad of risk factors, including potential impact on the public health, to direct its inspectional and import efforts. The import data system, for example, is so old and communicates so poorly with other FDA information systems that it is difficult for FDA officials to use risk as a predominant driver of their compliance efforts. Many of the data needs are obvious – such as what drugs are coming into the country from what manufacturers destined for what U.S. locations -- but the agency has been so starved for IT resources that it cannot do even some simple things with its current systems.

OTHER PRODUCTS

While I recognize that your focus for today's hearing is on prescription drugs, I would like to also briefly note that products other than foods and drugs are at risk from FDA's inability to adequately oversee imports. An ever increasing percentage of our over-the-counter drugs are being imported, often in final form without additional manufacturing in the United States. About two-thirds of our animal drugs are being made in China and

other developing countries, and FDA was able to conduct only 14 inspections of foreign animal drug facilities last year. And many Americans would likely be surprised to hear that a very large percentage – perhaps most – dietary supplements are produced in China as well (and a grand total of two of the foreign manufacturers of supplements received an FDA inspection last year).

I thank the Committee for holding this hearing today. Unfortunately, I was present for a similar hearing in this very room in 1986, and another in 2000. The concerns haven't changed all that much; but they're certainly more compelling than ever. I sincerely hope that this time your focus on this problem will result in some concrete action to help FDA protect our drug supply.

Thank you again for inviting me to give my views on this subject.

Mr. STUPAK. Thank you, Mr. Hubbard. Mr. England, please, your opening statement.

TESTIMONY OF BEN ENGLAND, SPECIAL COUNSEL, JONES, WALKER, WAECHTER, POITEVENT, CARRERE, & DENEGRE, LLP

Mr. ENGLAND. Mr. Chairman and members of the committee, I am Benjamin England. I am an attorney in the Washington, DC, offices of the law firm of Jones, Walker, 17-year veteran of the U.S. Food and Drug Administration. My bio is more fully explained in my written statement, which I would ask to be made part of the record.

Relevant to today's topic, I will only note that during my career Carl Nielsen and I participated in a series of imported counterfeit bulk drug investigations with Customs Enforcement in Newark, New Jersey, prior to the creation of FDA's office of criminal investigations. Some of those cases became of the topic of that hearing in June of 2000 before this committee. I am now an attorney in private practice. I represent domestic and foreign companies before and against various Federal agencies related to the manufacture, distribution, importation, and exportation of FDA and USDA-regulated commodities. I spent much of time assisting foreign companies and importers in complying with the myriad of Federal and State regulatory requirements prior to the process of importation to the United States. I do represent myself as a former FDA official interested in the matters before the committee.

At the outset, I will say I am very pleased that the committee has taken this issue up again and to focus specifically on the FDA's foreign drug inspection program, but as the Chair will know, this is not a new discussion. It has obviously been mentioned a number of times about the number of hearings that have been had on this particular issue. And I would also note that during the prior hearings we also discussed these imported counterfeit bulk drug cases. That New York Times article that published yesterday reported this rampant counterfeit active pharmaceutical ingredient, or API, industry in China, manufacturing not so fine chemicals and passing them off in Europe, South America, and Canada, and even the United States as legitimate product for drug manufacturing. These chemicals are manufactured in an uncontrolled and unregulated environment, as reportedly admitted by the industry participants and the Chinese government. True to the pattern, though, that Mr. Nielsen and I discovered in the early 1990s, these counterfeit and unapproved APIs make their way to the U.S. through third countries just as the Chinese manufacturer of the counterfeit gentamycin sulfate sent its bulk drugs to the United States through Europe. The stories of the Haitian children that were killed by DEG-tainted over-the-counter cough syrup, and now the more recent Panamanian incident, is all being reported as news. I daresay it is not news to the committee. It is not news to me, and it is not news to the FDA.

FDA's drug import program, its foreign drug inspection program, and its information technology systems, which are tasked with managing both and trying to integrate data, are broken. They were broken 8 years ago, and they remain broken today. FDA's current

import program is simply not capable of adequately assessing risks that may be associated with imported drugs, particularly given the ever-increasing volume, variety, and complexity of those drugs. One of the effects of free trade is the migration of manufacturing and processing to lower-cost markets. For FDA, that meant the answers to FDA's safety and quality questions about drugs, the real questions, which relate to how that drug is designed and how it is manufactured, and the environment in which it is made, cannot be found by border examinations in this country. You can't use a finished-product testing regime in order to assess that risk. Only boots-on-the-ground inspectors inside facilities can identify that.

Given the numbers of foreign manufacturers, processors, growers, storage facilities, exporters that send products to the United States, it is a foregone conclusion that FDA will never cross those firms' thresholds in any meaningful number or in any significant frequency. The question is, how can FDA get there more often to conduct these critical GMP inspections? And secondly, how can FDA obtain sufficient verifiable information about what is happening inside the manufacturing plant in China or in India or in Malaysia when FDA can't get there?

This foreign inspection problem and the import risks, the import program are conjoined problems. To be clear, one of the most important challenges I think FDA faces is lack of any efficient, real-time, risk-based, intelligent operational data screening system and its persistent siloing of agency data systems. Without correcting that problem, FDA could not even use the data that might emerge from more and more frequent foreign inspections. OASIS is only screening against preset data. It is not monitoring products that are imported. It is not evaluating those shipments for compliance with FDA requirements or for safety.

I think we all agree FDA needs a significant influx of resources. I don't want to discuss many numbers. I will simply note that the weakness of FDA's foreign drug inspection program is not really limited just to this 3,000 to 6,800 number. First, if you include the over-the-counter products, which is where we actually have had these reports of the safety risks, that number would be far, far greater. Then if we include foods and devices and biologics, the numbers skyrocket, and what we are left with to manage that risk is the import program, and the numbers that are involved in that program are even worse. Relying on that program leaves us with a more entrenched finished-product regime. It is critical that FDA get into more foreign firms that conduct good manufacturing practice inspections. Without more inspections, you can't even identify the risk baseline for drug imports, so you can't figure out where the baseline, as it dynamically shifts, where FDA should be focusing its resources in both the foreign inspection program and the import program. Both of these need to be repaired. The agency cannot use really any of the data it receives if it cannot integrate it and assess it, and that IT problem, if not fixed, will have us back here in 5 years with the same problem, except much more exaggerated.

Shortly after September 11, 2001, FDA's leadership council established an import strategic plan steering committee. By spring of 2003, that import strategic plan was virtually complete. FDA developed the ISP from contributions of more than 100 agency experts

and all product centers, field and headquarters components, laboratories, international program staff, general counsel's office, and the Office of Policy, Planning, and Legislation. I believe those ISP principles and many of those proposed solutions are critical to establishing a functional FDA program to integrate these foreign import and domestic operations, and then you have something to fund. Then you can target your resources, and you can identify and target new authorities. I also refer you to my proposals at the end of my written statement and look forward to a vigorous discussion on the important topic. Thank you.

[The prepared statement of Mr. England follows:]

Statement of

BENJAMIN L. ENGLAND, J.D.

Jones Walker Waechter Poitevent Carrere & Denegre, LLP

Before the

SUBCOMMITTEE ON OVERSIGHT & INVESTIGATIONS

COMMITTEE ON ENERGY & COMMERCE

U.S. HOUSE OF REPRESENTATIVES

November 1, 2007

1. INTRODUCTION

Mr. Chairman and Members of the Committee, I am Benjamin L. England, an attorney in the Washington, D.C. offices of the law firm of Jones Walker. I am a 17-year veteran of the U.S. Food and Drug Administration (FDA), during which time I held the positions of Regulatory Microbiologist in FDA's Baltimore Microbiology Laboratory, Consumer Safety Officer and Compliance Officer in FDA's Baltimore District Office, Special Agent with FDA's Office of Criminal Investigations in the Miami Field Office, Compliance Officer in FDA's Miami Resident Post, and Regulatory Counsel to FDA's Associate Commissioner for Regulatory Affairs (or ACRA) in Headquarters. I resigned my most recent FDA position as Regulatory Counsel to the ACRA in July 2003 -- a position I held in FDA for over three years as a Title 42 appointee. During my last three years at FDA, I was a key point person for Customs and Border Protection, I chaired the FDA's Counterfeit Drug Working Group, instituted the Joint Agency-Industry Working Group to combat product counterfeiting and tampering, which laid the ground

work for the preparation of FDA's initial Counterfeit Drug Task Force report, and co-chaired FDA's Import Strategic Plan Steering Committee.

I am now an attorney in private practice representing domestic and foreign companies before and against various federal agencies related to the manufacture, distribution, importation and exportation of FDA and USDA regulated commodities. I spend much of my time assisting foreign companies and importers in complying with the myriad of federal and state regulatory requirements prior to the process of importation into the U.S.

Along with my colleague, Mr. Carl Nielsen, who is also before you today testifying on his own behalf, I established the Agency's first series of Import Enforcement Training Courses, and with a few dedicated FDA and Customs officials, trained nearly every FDA import inspector, investigator, import program manager, and compliance officer in the effective use of Customs enforcement tools against products imported in the U.S. in violation of FDA requirements.

At the outset, I am pleased the Committee has taken up the issue of safety risks associated with imported products – and to focus today specifically upon FDA's foreign drug inspection program. But as the Chair will know, this is not a new discussion. Eight years ago FDA came before this Committee to answer questions about the very same topic based upon the Committee's thorough investigations into a series of imported counterfeit bulk drug cases initiated by FDA in the very early 1990s. The FDA's foreign drug inspection program, its import programs, and its information technology (IT) systems, which are overburdened with the responsibility of managing data about both, were broken then and, quite frankly, they remain broken today.

2. THE IMPORTED DRUG SAFETY CHALLENGES FACING FDA

It is important to provide some framework for this discussion. In an attempt to avoid duplicating the efforts of multiple witnesses I will keep my remarks to this end brief. Nevertheless, they are critical to understanding the balance of my testimony today. We must bear in mind that although we are discussing a very important concern – FDA's inability to inspect a sufficient number of foreign drug establishments for current good manufacturing practices (cGMP) compliance to ensure the safety of imported drugs – this topic still represents only one component of the entire import risk matrix confronting the agency.

FDA designed its current import program in the 1970s based upon a century old statutory regime. When section 801 of the Food Drug & Cosmetic Act (FDCA) was enacted very few FDA-regulated products were imported into the U.S. Prior to NAFTA and this country's participation with other international trade agreements, the majority of FDA-regulated imports consisted of ingredients and components intended for further domestic manufacturing. The most common inbound shipment consisted of break bulk (or noncontainerized) cargo arriving at seaports. The primary strategy at that time was to examine and test some products at the border but to primarily rely on FDA's domestic inspections to evaluate the quality of imported ingredients and components.

According to FDA data, from 1991 to 2000 FDA-regulated imports increased by 272% and in 2001 alone there were more than 7 million imported commercial lines of entry.[1] In 2002,

[1] A commercial line of entry is the equivalent of a line on a commercial invoice covering the sale of a product from a foreign exporter to a U.S. importer, owner, or consignee. A line may consist of a single laser DVD reader from Taiwan, regulated by FDA as an electronic product, or it may consist of 10 x 40 foot refrigerated containers of cantaloupes from Mexico. With regard to drugs, a line may be a shipment of 10 cases of retail ready over-the-counter (OTC) tablets of acetaminophen or a container of several metric tons of relatively pure bulk active pharmaceutical ingredients. A single invoice may have one or dozens of lines. FDA counts its import transactions by commercial line of entry. Each FDA-

approximately 7.8 million lines of FDA-regulated commercial shipments were imported. From 1997 to 2002, the number of imports of every kind of FDA-regulated product at least doubled. This year, in 2007, FDA anticipates as many as 18 million commercial lines of entry under its jurisdiction will be imported – representing a second doubling in the sheer number of entry transactions since 2002. FDA's resources directed at assessing the safety of imported products has remained static throughout the entire time period.[2]

Based upon my experience at FDA, which is further informed by recent statements from FDA in the press and in testimony before various congressional committees, roughly 60% of the total number of commercial lines of entry are food imports; 25% consist of imported medical devices; and 10% consist of imported drugs and biologics. Using these proportions, FDA is responsible for ensuring the quality, safety and efficacy of nearly 2 million imported drug shipments per year. These shipments range from small international courier packages containing several bottles of prescription pharmaceuticals to forty-foot container-loads of metric tons of bulk APIs for further manufacturing and processing.[3]

Since 1993, finished-product manufacturing in many FDA-regulated industries, including pharmaceuticals, has shifted to foreign markets. Now the answers FDA previously obtained

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regulated line is subject to FDA jurisdiction based upon the legal definitions of the various products in the FDCA.

[2] More regretfully, even though roughly half of all FDA-regulated products consumed in the U.S. are either manufactured in whole or in part in a foreign country, as I recall by the summer of 2003 approximately only 7 out of every 100 dollars spent by FDA regulating products under the Agency's jurisdiction was focused on FDA's import or foreign programs.

[3] This estimate does not include drug shipments received through the international mail system at the twelve international mail facilities around the country. Those small mail shipments are excluded because they are generally of a lower value and do not reach the threshold of a formal entry. The international mail system remains an un-automated, paper-based system and packages coming through it are not routed through FDA's electronic import screening system. They are off-line and virtually unevaluated for risk, unless a wary, experienced Customs official targets a package for further FDA review. However, even in those situations, FDA can review only a very small fraction of the packages targeted by Customs.

about the quality and safety of ingredients through its domestic inspection program lay thousands of miles beyond U.S. borders – and far beyond traditional FDA oversight. Yet FDA has continued to rely primarily on border examinations, label reviews, and a finished-product testing to identify problems with the vast majority of imported products under its jurisdiction.

In drug manufacturing, a product's ingredients are highly critical to ensuring finished product quality, safety, and efficacy. A remarkable amount of active pharmaceutical ingredients (APIs) are manufactured in foreign countries as are inactive (excipient) ingredients. FDA's foreign inspection regime may cover API manufacturing intended for application and prescription drug finishing, but for over-the-counter (OTC) products, the agency is virtually absent in the foreign market and at the border.

2. TEN YEARS' BACK

A. Defining the Universe

One particularly disconcerting issue that came to light during the hearings before this Committee in 2000 was FDA's inability to clearly identify the number for foreign manufacturing facilities exporting drugs to the U.S. For instance, FDA stated that it is "hindered by not having a complete list of foreign facilities manufacturing drug products for the U.S. market," which "indicate[d] a need to improve the Agency's information databases on foreign firms exporting drug products to the U.S."[4] This lack of a quantifiable foreign drug manufacturing universe completely undermines FDA's ability to assess the risks associated with products emerging from that universe. Further, it disables this Committee's capacity to conduct oversight.

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[4] *See* Statement of Dennis Baker, Associate Commissioner for Regulatory Affairs, FDA, Before the Subcomm. on Oversight & Investigations, Comm. on Commerce, U.S. House of Representatives, http://www.fda.gov/ola/2000/importeddrugs.html (June 8, 2000).

In 2000, FDA's list of "uninspected" foreign API manufacturers exporting to the U.S. ranged from 242 to 4,600, depending upon the criteria used to populate the list.[5] The reasons for such disparity include the FDA's multiple, "siloed", antiquated and non-integrated IT systems; the lack of a meaningful gatekeeper for the Agency's drug establishment registration process; the Agency's insistence to mitigate the usefulness of FDA's historical import entry (OASIS[6]) transactional data, and a redefining of the very term in question: "uninspected foreign firms." Ordinarily, FDA answers this question with respect to "foreign drug firms that *should be* inspected by FDA." Following that framing, FDA typically characterizes the question as solely relating to foreign firms manufacturing prescription or application[7] finished drugs or APIs. This recharacterization alone results in a substantial downward departure of the magnitude in the number of foreign firms of regulatory significance.[8]

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[5] *See* Statement of Jane E. Henney, M.D., FDA Commissioner, Before the Subcomm. on Oversight & Investigations, Comm. on Commerce, U.S. House of Representatives, http://www.fda.gov/ola/2000/counterfeitdrugs.html (Oct. 3, 2000).

[6] "OASIS" is an acronym that stands for FDA's "Operational and Administrative System for Import Support." See FDA's discussion of OASIS at http://www.fda.gov/ora/import/oasis/home_page.html.

[7] Application drugs include those that are subject to an FDA New Drug Application (NDA), Abbreviated NDA (ANDA), New Animal Drug Application (NADA), or Abbreviated NADA (ANADA). It also may apply to Investigational New Drugs (INDs) depending upon whether the agency is seeking to promote an expansive view (*e.g.*, the scope of its jurisdiction under the law) or minimalist view (*e.g.*, its inspectional duties under the law). In many cases, the same API may be used for manufacture of an application or non-application drug (*e.g.*, an OTC drug product) or in the human or animal drug market.

[8] Note that on the same date as Dr. Henney's October 2000 testimony (*see* n.7) FDA created, populated, and issued an Import Alert affecting the smaller number (242) of these foreign API firms. In FDA's own opinion the Agency could not determine from a review of their own internal data systems that these 242 firms had ever been inspected. *See* Detention Without Physical Examination of APIs that Appear to be Misbranded Under 502(f)(1) Because They Do Not Meet the Requirements for the Labeling Exemptions in 21 C.F.R. 201.122, at http://www.fda.gov/ora/fiars/ora_import_ia6666.html (issued Oct. 3, 2000, last updated Aug. 25, 2006). The body of that import alert contains a clear example of the agency's recharacterization to reduce the size of the uninspected foreign firm universe. The alert states, "OASIS records indicate that a large volume of bulk chemicals which can be used as APIs in human medicines *that require NDAs, ANDAs, or INDs* are being offered for entry into the U.S." *See id.* FDA then exempts from the guidance in the alert those APIs intended to for pharmacy compounding (whether of a

Today, it is apparent that all of these factors persist at FDA and the agency is still struggling to identify the scope of the universe of foreign drug firms under its jurisdiction – whether we speak in terms of all foreign firms exporting drugs for human or animal consumption or merely foreign firms that FDA believes "should be" inspected. Lacking the ability to identify the larger, total universe of foreign drug firms exporting drugs to the U.S., the attempt to reduce that total to a more manageable "high risk" universe for targeting inspections has little foundation in reality. Consequently, FDA's current range of foreign drug firms exporting drugs to the U.S. that *should* be inspected by FDA is from 3,000 to 6,700.[9]

B. Identifying and Assessing FDA's Tools for Managing Imported Drug Risks

In 1998, the Government Accounting Office (GAO)[10] reported that FDA relied on "15 separate [data] systems to identify foreign pharmaceutical manufacturers, plan foreign inspection travel, track inspection results, and monitor enforcement actions." FOOD AND DRUG ADMINISTRATION: Improvements Needed in the Foreign Drug Inspection Program, GAO Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives, at http://www.gao.gov/archive/1998/he98021.pdf (Mar.

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prescription or OTC finished drug) or for manufacturing into an OTC drug product. Ironically, a manual count of the number of firms on FDA Import Alert 66-66 reveals that today there are currently 243 firms subject to the alert's regulatory guidance.

[9] These numbers are derived from two separate FDA data systems and thus the disparity. The lower number is reportedly from FDA's Drug Registration and Listing System (DRLS). The higher number is a downward departure from data stored in ORADDS, the OASIS data warehouse. Therefore, the lower number is taken from the process whereby foreign manufacturers report data to FDA in order to meet two of the most basic minimum requirements to export drugs to the U.S.: drug registration and drug listing; and the higher number is taken from the process whereby Customs brokers report to Customs and to FDA through OASIS the identity of foreign manufacturers *actually* exporting drugs to the U.S. This discrepancy alone is troubling. It is unclear over what time frame the two numbers were derived and whether they correlate. Further, it undercuts FDA's traditional argument that OASIS data is unreliable simply because it represents self reporting through the importation process. DRLS also represents self reporting to FDA, and in the import declaration environment, there is another agency, Customs and Border Protection, that strictly governs and enforces proper data reporting.

[10] Since renamed the "Governmental Accountability Office".

1998). This is, in large part, a continuing problem at FDA. These multiple "siloed" IT systems were created for disparate reasons, and therefore, they house and track data in formats that render them of limited value to import inspectors, compliance officers, and the Agency's foreign trip planners and foreign inspection schedulers. It is clear that they still produce widely varying results when used to identify the universe of foreign drug firms of regulatory significance. The lack of integration in FDA's IT systems to a great extent is a result of a lack of integration within the agency itself. Consequently, FDA's IT systems are built around its organizational stove pipes, resulting in systems that are not designed to talk to each other and are not formatted to dispense data upon inquiry to support programs in other branches of the agency.

The GAO also reported in 1998 that "FDA conducts infrequent routine inspections of foreign [drug] manufacturers to ensure that they continue to comply with U.S. quality standards, although routine [cGMP] surveillance inspections constitute FDA's most comprehensive program for monitoring the quality of marketed pharmaceutical products." While the number of foreign firms exporting drugs to the U.S. increased during the 1990s, the agency's foreign inspections and resources for import operations (and, incidentally, its IT budget) remained disproportionately static or dwindled. The FDA's inspection cycle for drug firms in India and China, by way of example, was reported in the 1998 GAO report to run between 4 and 5 years, in contrast to the domestic industry, which was (and is) inspected nearly every other year.

Today, using the smallest FDA inventory estimate of 3,000 foreign drug establishments that *should* be inspected (*e.g.*, prescription and application drugs and API manufacturers), maintaining a 5-year surveillance, cGMP inspection cycle would require FDA to conduct 600 such inspections annually. I find no one who reasonably argues this number of foreign inspections is attainable at FDA's current resource level or as long as the agency spends the vast

percentage of its resources on domestic industry compliance. Achieving a more appropriate 2-3 year inspection cycle among this same population would require FDA to conduct approximately 1,250 (on average) foreign surveillance, cGMP inspections per year. In addition, for the Agency to be capable of assessing the compliance status of foreign firms *between* inspections would require a complete reinvention of the agency's import program and IT systems.

Fundamentally speaking, the import and IT reinvention process to better manage risks associated with imported drugs cannot be limited to the resources available to conduct foreign inspections. Otherwise, FDA will continue to cast its foreign inspection risk assessment/mitigation net just wide enough to capture the narrowest and highest therapeutic or manufacturing process risks, such as prescription drugs or sterile manufacturing processes. Instead, the questions should be: "Which foreign facilities should be inspected? And which import shipments should be intercepted based upon **all** available risk data?" Answering either question using only 3,000 to 6,700 prescription or application foreign drug manufacturers as your universe presumes OTC drug shipments are low risk – but that is purely a presumption. Where this presumption persists the diminishing percentage of inspected foreign firms vs. those that *should* be inspected results in a substantially smaller and arbitrarily defined failure to manage imported risk.[11] Consequently, legislating or funding into this presumption excludes

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[11] The GAO observed the same problem when discussing this issue with FDA in the 1990s. In the 1998 report, the GAO states,

> In developing its new four-tiered [foreign] surveillance inspection strategy, however, FDA did not include all foreign pharmaceutical manufacturers that it should consider for a routine surveillance inspection. According to FDA data, *about 3,200* foreign manufacturers have submitted information to FDA listing pharmaceutical products that they intend to export to the United States. However, FDA prioritized for routine surveillance inspections only the 1,100 foreign pharmaceutical manufacturers that it had previously inspected. Consequently, FDA's scheduling strategy does not account for almost two-thirds of the foreign manufacturers that may be exporting pharmaceuticals to the United States.

risks that are likely quite substantial. Further, it perpetuates the problem the Committee has been trying to resolve for at least the last ten years.[12]

When FDA is virtually absent in the foreign market assessing compliance with cGMPs, the Agency is left with attempting to assess risks associated with foreign sourced drugs and drug ingredients using its import operations. The import program, however, focuses primarily on FDA approved application, facility registration, and drug listing database submissions, label reviews, and finished product testing. These approaches are woefully inadequate to assess the cGMP compliance and therefore the quality and safety of imported drugs. Although testing can tell FDA something about the quality and even the safety of an imported product, finished product testing at the border (or anywhere along the supply chain) is not a statistically valid method for predicting the safety of later or earlier untested shipments – even other shipments from the same processor.

Where product (and patient) safety is so dependent upon an ongoing and rigorous manufacturing quality system, finished product testing is not even a valid way to determine product safety within the same shipment. Compliance with FDA's drug cGMP program is the only (current) framework within which the agency can justify relying upon the results obtained from finished product test. Finished product testing is confirmatory only. Without an assessment and understanding about the conditions of manufacture within the facility, the

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GAO Report at 26 (emphasis added). Ironically, ten years later FDA is doing the same in its reporting to GAO and this Committee, except now the number of facilities that *should* be inspected has itself risen to 3,000 to 6,700 establishments. Of course, FDA has since abandoned its four-tiered targeting strategy for foreign firms because it never got around to inspecting tiers III and IV and so there was no purpose in distinguishing among them. Today we learn that FDA has 600 foreign drug firms identified in its systems that are making and exporting "unknown" drugs.

[12] Take, for example, the numerous press accounts and FDA notices regarding the presence of diethylene glycol (DEG) contamination (or substitution) in glycerine-based drug ingredients or finished products – all of which were discovered in OTC drugs or non-active drug ingredients (excipients).

finished product test results are anecdotal at best. Such an approach cannot predict, measure, assess, or assure drug safety.

Any question about this premise is laid to rest with a simple hypothetical observation: If, during a facility inspection, FDA were to find a drug company's cGMP program rested upon establishment registration, drug listing, labeling compliance, and finished-product testing the Agency would shut the facility down, seek a mass seizure, force a (voluntary) recall, pursue civil disgorgement and probably criminally prosecute its operators. Yet, to the greatest extent, that is the near equivalent of FDA's current imported drug evaluation program. Lacking a robust foreign drug inspection program, which takes into consideration all elements of prescription *and* non-prescription foreign drug manufacturing in its scheduling and preparation, promotes a "catch me if you can" foreign drug compliance culture.

3. FDA's Recent Public Discussions Regarding Imported Product Risks

Before I discuss proposed solutions to the drug importation problems, I would like to note a few additional examples where FDA is attempting to redefine what it is currently doing as "risk management." For instance, I have previously noted in similar settings that FDA has implied its import electronic screening system (OASIS) is assisting in assuring the safety and compliance of imported products – but it is not. OASIS is a static, hard rules based system. It only looks for things it is specifically instructed to look for among data elements derived primarily from an invoice, shipping manifest or bill of lading. Such documents simply do not contain information about the manner in which a product was manufactured or the ingredients or components used to prepare the product.

The most common OASIS preset screening combinations are shipper or manufacturer identity plus FDA product code or country or region plus FDA product code. These data

combinations are used to implement FDA's import alert system. However, even when an import alert "hits" in the system, a human entry reviewer must still physically read through dozens of pages and scour through perhaps hundreds of written data elements to see if OASIS is correct before automatically detaining a shipment based upon the alert. OASIS is not integrated with other FDA legacy systems; therefore, import inspectors, import entry reviewers and import compliance officers must enter and exit dozens of data bases in any given hour to determine whether data submitted through OASIS is accurate and truly applicable to an imported shipment. The waste in full time equivalents is probably incalculable and FDA's current resource management systems do not capture this waste. Although OASIS assists in work flow management and tracks import transactions, it performs no affirmative compliance or safety assessment. Furthermore, the import alert system is only risk based to the extent that it "hits" for further review shipments that correspond to data already determined by a prior import examination. Each Import Alert is populated by evidence of situations that have already been discovered. Therefore, the system does not assist FDA in targeting future inspections. [13]

Recently, FDA admitted these facts during a hearing before the Subcommittee on Agriculture Appropriations in the House Committee on Appropriations.[14] Yet, FDA persists in claiming that the agency "currently screens electronically-submitted information on all incoming shipments, and then uses a risk-based approach which targets [FDA's] inspectional resources at

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[13] Although Import Alert data, based upon prior FDA foreign inspections, is integrated into OASIS, that screening is not based upon prospective risk management but is a reactive implementation of already discovered problems. It is good the Agency has integrated Import Alert screening into OASIS, but it is not the kind of risk assessment that helps FDA determine what to inspect next.

[14] During this hearing Dr. Steven M. Solomon, FDA's Deputy Director of the Office of Regional Operations in the Office of Regulatory Affairs, acknowledged that my characterization was fundamentally correct. Sept. 25, 2007.

products having the greatest potential for causing harm to public health."[15] This latter assertion implies that FDA has developed a risk-based approach for assessing and targeting incoming imported products for the greatest potential for causing public harm and then applies that risk-based approach to the electronically (OASIS) submitted data. The two assertions cannot coexist. OASIS lacks the capacity to evaluate any imported data, irrespective of product, country of origin, manufacturer, or FDA requirement. Therefore, the only screening that can be occurring in OASIS is based upon the invoice data submitted into the system and preset rules, as defined by prior examinations (import alerts), drug registration and listing, and invoice data, which have no relation to compliance of the foreign drug manufacturer on most important drug quality, safety, and efficacy level – cGMP compliance.

This mischaracterization of the capabilities of FDA's IT systems carries over to its implementation of the "Bioterrorism Act"[16] requirement to for food importers to provide prior notice of imported food shipments and the Agency's explanation of what the International Trade Data System was designed or is capable of doing. FDA states, for example, "[o]ne of the most important provisions [of the Bioterrorism Act] is the requirement that FDA be provided prior notice of food (including animal feed) that is imported . . . into the U.S. This advance information enables FDA, working closely with [Customs and Border Protection], to more effectively target food that may be intentionally contaminated with a biological or chemical agent or which may pose a significant health risk to the American public."[17] FDA fails to

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[15] *See* Statement of Steven M. Solomon, D.V.M., M.P.H., Deputy Director of the Office of Regional Operations, Office of Regulatory Affairs, before the Comm. on Ways and Means, Subcomm. on Trade, at http://www.fda.gov/ola/2007/importsafety100407.html (Oct. 4, 2007).

[16] *See* Public Health Security and Bioterrorism Act Preparedness and Response Act of 2002 (Bioterrorism Act), Sec. 307, P.L. 107-188, June 12, 2002.

[17] *See* Solomon, *supra* n. 12.

address the fact that the prior notice submission amounts to little more than the invoice data that already appears in the electronic entry submitted to OASIS – plus some arrival and facility registration information. The food facility registration program, however, suffers from the same weaknesses as the drug registration program – it is entirely disconnected from manufacturing and processing data and there is no registration gatekeeper on the portal. Any of us could register ourselves as foreign drug, device, food, or cosmetic manufacturing facilities – or all four – and obtain the registration numbers.

As stated previously, these challenges to identifying, assessing and mitigating or interdicting risks associated with imported products did not arise recently. Yet contrary to all logic a post-NAFTA FDA has continued to pursue a doomed pre-NAFTA paradigm. It is even more troubling that FDA has failed to implement literally hundreds of proposed solutions to specific import and foreign inspection problems which would have enabled FDA to begin to progressively focus its limited resources where the risks are indeed greatest. Those proposals were made internally through the Import Strategic Plan (ISP) over four years ago. In the meantime, FDA regulated imports again increased from approximately 10 million to 18 million commercial lines of entry.

Given these circumstances, increasing funding to support FDA's current import and foreign drug inspection programs, without requiring a significant change in its approach would, in my opinion, produce far additional waste, result in even more shipping delays for compliant and safe import shipments, and provide little basis for consumer (or congressional) confidence in the safety of imported drugs. Attempting to build on existing efforts and operations is predestined to fail because it would be based upon too many false presumptions. A drastic internal change is needed.

4. The Bioterrorism Act

On June 12, 2002, President George W. Bush signed the Bioterrorism Act into law and dramatically enhanced FDA's import authority for imported *foods*. Most notably, section 302(a) of the Bioterrorism Act amended Section 801 of the FDCA directing FDA to give "high priority to increasing the number of [import] inspections . . . for the purpose of enabling [the agency] to inspect food offered for import at ports of entry into the United States, with the greatest priority given to inspections to detect the intentional adulteration of [imported] food." Furthermore, section 302(b) directs FDA to "improve its information management systems that contain information related to foods imported or offered for import into the United States for purposes of improving the ability of [FDA] to allocate resources, detect the intentional adulteration of food, and *facilitate* the importation of food that is in compliance with [the FDCA]." 21 U.S.C. § 381(h)(2).

This second legislative mandate essentially establishes the framework within which the balance of the new food safety and security authorities were to be implemented. More significantly, this subsection provided a blueprint for the agency to redesign its import policies, programs, and operations through the ISP process. FDA has persisted in ignoring these mandates for imported foods. Perhaps by Congress' reiteration of this principle for imported drugs, devices, and cosmetics, the agency would understand how the provision relates to international risk management; by incorporating a comprehensive risk-based foreign inspection regime for all drug facilities and quantifying the risk-mitigation value of other regulatory programs already being pursued by the agency and industry. In my opinion, 21 U.S.C. § 381(h)(2) should be extended to all FDA-regulated imported commodities, including imported drugs. With such language, the industry would be empowered to present to FDA ways that

foreign sourced drugs can be demonstrated as safe and effective and of appropriate quality, enabling FDA to focus its foreign inspection and import oversight resources where the risks are greatest.

5. The Import Strategic Plan

A. Missed Opportunities for Change

One of the most important messages today is that FDA's foreign drug inspection program is only one means for FDA to assess and mitigate risks related to imported drugs. Foreign sourced drugs, whether finished or ingredients, active or inactive, must also pass through the bottleneck of FDA's and Customs' import assessment. Although it is true that FDA's import program is woefully inadequate today, only addressing imported drug risks in terms of increased foreign inspections leaves open risks that may arise in between foreign inspections – even if conducted o every 2-3 years, or in the product supply chain (*e.g.*, product counterfeiting, commingling, or tampering). Further, as FDA will never cross enough foreign thresholds to enable the Agency to apply inspection data on all imported drug shipments – more than additional resources for foreign inspections is needed.

Shortly after September 11, 2001, FDA's Leadership Council established an Import Strategic Plan Steering Committee. By spring 2003 the Import Strategic Plan was virtually complete. FDA developed the ISP from the contributions of more than one hundred Agency experts in all product Centers, field and headquarters components, laboratories, international programs staff, the General Counsel's Office and the Office of Policy, Planning and Legislation.

The ISP's principles were simple but far reaching: Push the current FDA import evaluation process from the extremely limited border transaction to a life-cycle process, which:

- Intentionally gleans information from all points along an article's supply chain;

- Assesses that information based upon FDA requirements and risk of harm;
- Delivers the assessment to border inspectors, compliance officers, and electronic screening systems for reliable targeting decisions; and
- Results in the facilitation of safe products and enforcement against products that are unsafe.

Under the ISP, three subcommittees were created to assess import safety risks and propose agency solutions along the component parts of the international supply chain, including: foreign operations, border operations and domestic operations. Two cross cutting subcommittees were tasked with tying these supply chain components together: Information Technology and Applied Science and Technology. Each committee was to find information FDA could use to assess risk and develop solutions for mitigating risk earlier in the supply chain rather than later. Meanwhile, the IT and Science subcommittees identified solutions implementing the proposals and reducing time frames where risk targeting indicated a need to inspect and test incoming goods. At the request of the Leadership Council, the ISP subcommittees and steering committee value-ranked the proposed action items for enhancing import safety and estimated their costs as of Spring 2003.

The significance of the ISP and its proposed action items rests in what it represents: an internal agency demand for a dramatic shift in thinking about the identification, assessment and mitigation of risks in the international supply chain. Many of the ISP proposals are indeed costly. However, many could have been implemented nearly immediately and would have begun the process of increasing FDA's import efficiency and effectiveness using existing resources. It is this shift in thinking that FDA's middle and upper management has resisted. But

I believe that all involved in the ISP process recognized the import problems – even in 2003— are complex and cannot be solved with FDA's traditional regulatory approaches and philosophy.

B. Some Proposed Changes Going Forward

First, any action by this Subcommittee should include a significant resource investment targeted directly for reengineering FDA's stove-piped IT systems. IT improvements recommended in the ISP are a contingency for executing any serious risk-targeting strategies for foreign inspections and import interdiction of unsafe drugs.

Second, I recommend the establishment within FDA of an organization reporting to the Commissioner with the mission of focusing on enhancing the safety of imported products – all products. We believe fixing FDA's import and foreign inspection problem requires it be broken free from the domestic programs, which produce much of the bureaucratic inertia against change in this area. A new organization would enable proper staffing, allocation of human resources at ports of entry, management and implementation of ISP-based strategies. It should be responsible for all import and international focused work-planning activities; conducting facility inspections of foreign processors and importers; overseeing and conducting border operations; conducting foreign government and industry assessments and training; and support trade negotiations in a manner to enhance safety of imported products. To accomplish this, the new organization should be directly funded, rather than receiving its funding through the product Centers. A basic persistent infrastructure to manage risks associated with all imported commodities must be maintained regardless of year-to-year changes that may appropriately occur in program directions.

Third, section 302(b) of the Bioterrorism Act, which enables FDA to implement risk-based strategies for managing food imports, should be expanded to cover all other FDA-regulated products including drugs.

Fourth, FDA should publish and begin implementing the ISP in accordance with the plan's guiding principles, goals, and themes.

Fifth, FDA should begin developing programs for obtaining information from third parties about the cGMP compliance status and supply chain security programs of foreign drug facilities that are *not* inspected by FDA. This additional risk data may come in the form of third party inspection and certification companies, accompanied by a robust auditing process on both sides of the border, foreign inspectorates, or other U.S. Government Agency inspections and information. Obtaining and assessing all available risk data would enable FDA to (a) better target its foreign inspections; (b) interdict and examine high-risk imported drug shipments (related to product safety); (c) follow up in the domestic market those shipments that proceeded through the border with inadequate inspections; and facilitate imported drug shipments that are likely to have been manufactured in accordance with FDA's cGMP requirements. This would permit the agency to focus its most earnest import inspection and examination efforts on shipments representing known and unknown risks.

Sixth, FDA requires additional resources to conduct more foreign inspections and import examinations and to develop and publish meaningful Agency guidance relating to identifying and managing risks in the full life cycle of imported products.

Seventh, FDA should rely on Customs and Border Protection and the Department of Homeland Security (DHS) to manage security risks associated with FDA regulated imports. DHS' security programs should be expanded to incorporate *product* security risks (such as

product counterfeiting and tampering) rather than focusing solely upon the security of in-transit cargo or inbound containers.

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I thank the Subcommittee Chair and Members for the opportunity to discuss these important issues and we look forward to answering any questions.

Mr. STUPAK. Thank you, Mr. England. That concludes the opening statements of our witnesses. We will begin with questioning. We will go for five-minute rounds on questioning. Dr. Crosse, on page 13 of your testimony, you note, and I quote, "The FDA's data indicate that some foreign drug manufacturers have not received an inspection, but the exact number of establishments not inspected was unclear." In fact, you note that there are more than 2,000 foreign establishments for which the agency could not identify previous inspections. Where are these firms? Who are these firms? What are they shipping? What risks do they pose, and what does it mean that there is no record they have ever been inspected?

Ms. CROSSE. Well, as to who are these firms, where are they, and what are they shipping, we don't know, and I am not certain that FDA knows.

Mr. STUPAK. Have you asked for the information?

Ms. CROSSE. We are still continuing our work for the committee to try to understand in greater depth the nature of some of these problems and what kind of enforcement actions FDA has been taking. The data about the number of establishments that may never have been inspected are coming from one of the many data systems that they have. This is from their risk-based model, where they had between 3,200 and 3,300 establishments that they assessed, to prioritize those for their routine surveillance inspections. Those records, as part of the risk assessment, examine whether or not there has been a recent GMP inspection at a facility. Over 2,000 of those establishments had no inspection indicated in that system.

Mr. STUPAK. Did they have a pre-approval inspection?

Ms. CROSSE. Not clear from these data, but because some of the establishments included in this risk-based prioritization system are those that have registered and may never have imported a product into the United States—so their risk model is not necessarily built on the base of firms that are sending product here.

Mr. STUPAK. Well, we all talked about that in a lot of the discussion about prescription drugs or active pharmaceutical ingredients, but that also includes, does it not, over-the-counter drugs that you don't need a prescription for? You just go in the drug store and buy it? Like the toothpaste with the DEG that was found?

Ms. CROSSE. Yes. In their——

Mr. STUPAK. FDA has responsibility to inspect those facilities where they are manufactured?

Ms. CROSSE. That is correct. FDA is responsible for inspecting all of those facilities. In their risk-based model, they consider over-the-counter manufacturers to be of lower risk than those producing certain types of prescription drugs.

Mr. STUPAK. Well, let me just ask this panel or anyone who cares to answer it, there has been a movement, and I know it has nothing related to this hearing directly, but indirectly it does, there has been a movement to put a third class of drug. You have prescription drugs, you have your over-the-counter drugs, now there is this movement to make the BTC or behind-the-counter drugs. If we do that, a third class, is that just opening up to more drugs with less inspections, or more drugs with, we have no idea what they are?

Ms. CROSSE. No, sir, I don't believe that is the case. My understanding of the third class of drugs is that some current drugs that

are marketed, either over-the-counter or primarily those that are prescription drugs, would simply move to a behind-the-counter status, where you would have to have some interaction with the pharmacist in order to obtain the drug. Not that it would add a whole new category of drugs that don't currently exist into the marketplace, would just regulate some of them differently.

Mr. STUPAK. OK, thanks. Mr. England, I was really intrigued with your import strategy plan when 2003 recommendations were made to the FDA on what should be done, and this was, I think, Mr. Nielsen, were you involved in that also, the import strategic plan?

Mr. NIELSEN. Yes, I was.

Mr. STUPAK. That was right after 9/11. That was what you were referring to? How do we—What ever happened to that? Either one, Mr. England or Mr. Nielsen, or Mr. Hubbard, if you know, if you were a part of—were you a part of that group, too, the ISP?

Mr. HUBBARD. Yes, I was.

Mr. STUPAK. What ever happened to it? 2003 was recommendations made to finalize their plan. What happened to it?

Mr. HUBBARD. Well, the commissioner at the time was faced with, as I said, he was faced with tremendous priorities elsewhere and felt that to do that plan, while it was a reasonable plan, there was simply no funding for it, and he didn't believe that a request for funding would be welcome at that point.

Mr. STUPAK. Would be welcome by the administration or by the Congress?

Mr. HUBBARD. Well, whomever. The FDA had so many other priorities at the time that he basically said, look, I think you guys are on the right track here, but I would have no way to fund this, and we can't do it without funding. But I do understand the agency has been trying to do pieces of it——

Mr. STUPAK. Well, that is what I was just going to ask Mr. England, since you brought it up in your testimony. There were pieces of this ISP, Import Strategic Plan of 2003, that could be really implemented with little or no cost, right?

Mr. ENGLAND. That is true.

Mr. STUPAK. Give us an example.

Mr. ENGLAND. Well, I will give you an example. When FDA conducts a foreign inspection and goes in the country, you know, FDA receives registration data from foreign facilities. They may be food facilities, or they may be cosmetic facilities on a voluntary basis, they might be medical device or drug facilities. The discussion ensued during the development of the ISP that one of our weaknesses in the agency was that there was no real gatekeeper on the registration process. No one knows who these people are, and so during foreign visits, would it not be possible for a foreign inspector to perhaps stay an extra day, take the addresses, and at least identify the facilities that are listed in the addresses for the registrations actually exist, or that there is not an apartment complex there? I mean, just some basic verification of data while inspectors are in the country. They are already there to do a foreign inspection anyway. But those would be the kinds of examples. The other examples might be to rely upon data that other U.S. government agencies have from foreign inspections they conduct. You know,

there are inspections that are conducted by other agencies of foreign seafood processors, of bottled water manufacturers, of, you know, where there are contracts that are let by another government agency. Another government agency may sub-contract an inspection process prior to procurement. That data is actually out there and could be used for integration into the FDA import process. I think the biggest problem we ran into, though, was, how do you integrate the data, because the IT systems were so broken.

Mr. STUPAK. Right. It is in shambles. Mr. Hubbard, my time is up, but I want to ask you this. You have been at the FDA, you said 30 years. You talked about the 1986 hearing. You talked about the 1998 GAO report, the 2000 hearing. Now we are here in 2007. What happens internally? I mean, we have these hearings. You were in one of the key positions in the FDA, especially 2000. I remember that one clearly because I was here, the 1998 report. What happens? We hear these promises. Things will be different. We will fix the IT system. It goes back to the FDA, and all this testimony and all this just goes in the circular file, or what?

Mr. HUBBARD. Well, I share your frustration, Mr. Chairman. I think it comes down to resources. The program has always been a poor little sister there at FDA. It has never gotten resources. Even now, they only devote a little over 100 FTEs a year to these folks' market issues, so to me it is resources. I think there needs to be some funding provided if it will fix the problem. To me that is the big missing piece, is the funding.

Mr. STUPAK. But, again, going back to your experience, but what happens on the resources? I mean, I don't ever remember the FDA coming up pounding on the table before the appropriators, saying, we need this, just from a safety point of view, to protect America. We need these resources. Is the gatekeeper of the resources request the administration? And if the administration doesn't make it a priority, it doesn't put the resource request in?

Mr. HUBBARD. If you look at the last 10 or 15 years, the president's budget usually gets funded, but if it doesn't get in the president's budget, Congress never adds more. And the president's budget has been very strict on FDA in recent years.

Mr. STUPAK. Mr. Whitfield, questions, please. Thank you. We are probably going to go more than one round here.

Mr. WHITFIELD. Well, we appreciate all of you being here today, and certainly all of you all are experts at the FDA. Three of you worked there for many years, and you have attended enough of these hearings and expressed the frustration in your own testimony, and obviously lack of dollars is one of the big issues. And, would you all agree with that? OK. And in addition to that, would you elaborate on some other obstacles, just from your experiences. I mean, is there a culture over there that has something to do with it? I know that one of you mentioned that the most serious issue was a lack of a risk-based data screening system that really works. But if each one of you would just. You have all been involved in coming up with new plans. As you say, every 2 to 3 years we are back here talking about the same problem. So, lack of money is one big issue, and would each one of you maybe elaborate on a couple of other things? Dr. Crosse.

Ms. CROSSE. Well, I haven't been in FDA, but it is certainly true that resources is a major constraint here. It also seems to me, though, that because of the resource constraint the approach has been, OK, we can't do it all. Let us work backwards at this. Given the regulatory requirements, the statutory requirements for inspections, we have only got this many resources. How many can we do, and then do some figuring on where you can go within that, rather——

Mr. WHITFIELD. We can't do everything, and——

Ms. CROSSE. We can't do everything, but rather than trying to make an assessment, it appears there has been no attempt to try to make an assessment of what the universe is and to try to integrate the information and start from that end to assess the risks that are the largest and to try to manage from that side.

Mr. WHITFIELD. OK. What about you, Mr. Nielsen?

Mr. NIELSEN. I think the biggest obstacle is the current organization is the original organization, totally organized not for the international market. Even the location of the facilities, or because of the location in a judicial district, not because of incoming products. Then, on top of that, because of the existing system largely being oriented to overseeing the domestic industry, the work planning process is not designed to deal with the international difficulties, either. And so it is also my contention that the organization stove-piping is what causes our IT stove-piping, and that is why I believe part of the real solution is it really is an organization designed for all of these problems we have been talking about for over a decade. And then the requirements and the solutions can be realized and I believe can be implemented with the appropriate funding.

Mr. WHITFIELD. OK. Mr. Hubbard.

Mr. HUBBARD. Well, someone suggested the way to solve this would be some forms of memorandum of agreements with other countries in which they step up and do a better job, and conceptually I think that is a good idea, but take China as an example. The Chinese are suffering 200,000 to 300,000 deaths a year from sub-standard and counterfeit drugs, among their own people.

Mr. WHITFIELD. 200,000 to 300,000?

Mr. HUBBARD. Yes, that is an estimate that is out there, and my point is, if they can't protect their own people, I don't think we can depend on them or any other country to protect us. I think we need to protect ourselves.

Mr. ENGLAND. Yeah, I would, if I could, just build quickly on what Mr. Nielsen and what Mr. Hubbard both said. This idea of culture is a persistent issue in the agency, and I can recall when I left the lab in Baltimore and went into investigations, and I went into the import operations group, the supervisor I worked for in the lab asked me if I was nuts. He said he realized it is a dead-end job to go work in imports. And then, a couple years later, NAFTA was passed, and then we began to see these increases in imports became more significant, and the foreign market became more significant. So timing was good on my side. I don't propose to have any gift of prophecy, but it has worked out. But I think that that persists. I mean, imports and the foreign program largely is still essentially this red-headed stepchild. A very small percentage of the dollars that FDA expends are expended on the foreign source

market. In 2003 the number was about $7 out of every $100 was based on imports or foreign, so it is a very small number. I don't know what it is now, but that was the number that I received then. I think that, in order to try to address it, though, organizationally, this framework problem does call for the need for an organization within the agency that does have the responsibility. They have got the line-item budget authority. They have got the ability to manage the field assets. Some things that report into the commissioner level, that it is the import foreign program, and from that can come information sharing, but they also have to have this IT system that is also integrated, and it can't be just about drugs. It has to be about drugs and foods and devices and biologics. So you really are talking about a rather substantial reorganization in the agency in order to create the line of authority and the budgeting in order to actually drive the process.

Mr. WHITFIELD. Just one quick question. You mentioned this Haiti, the children in Haiti. How many children died in that incident?

Mr. ENGLAND. I don't recall. There was a couple hundred. I don't recall.

Mr. HUBBARD. Well, in Haiti, I believe it was 86, and Panama I believe it was in the 40s, but it was a lot of kids with clearly a substitute of antifreeze, that we put in our automobiles, for a legitimate drug.

Mr. ENGLAND. And in my understanding, that product was found here eventually and had to be recalled. And so it is almost as if we are waiting for these deaths to occur in other countries, and then we go looking for it. Whereas, as Carl points out, I think in his written testimony, that GMPs would have addressed that issue. That is a GMP—that is an incipient ingredient processing issue that happens to be in an OTC manufacturer, so whether there is oversight there is a different question, but——

Mr. STUPAK. Right. We used this chart before on this, and I know Mr. Whitfield is familiar with it, the DEG that they put into the toothpaste in both Panama and Haiti but also found in our toothpaste here in this country.

Mr. ENGLAND. That is correct, so——

Mr. STUPAK. Mr. Dingell, for questions, please.

Mr. DINGELL. Mr. Chairman, I would like to commend the panel. This is one of the best panels we have had in this committee, and I want to thank you for your quality and vigorous testimony and for your help to us. I have a limited amount of time, so we have to deal with this very quickly. Mr. Nielsen, you are the former director of imports in FDA, with 28 years of experience. Isn't it true that FDA can provide a meaningful figure on the number of firms shipping drug products to the United States because of outdated databases?

Mr. NIELSEN. Yes.

Mr. DINGELL. Mr. Nielsen, FDA doesn't have a good handle on this inventory, do they?

Mr. NIELSEN. That is correct.

Mr. DINGELL. Mr. Nielsen, since FDA can't calculate the total number of foreign firms that are shipping drug products to the

United States with any precision, how can we have confidence that the agency is truly managing risk?

Mr. NIELSEN. You can't.

Mr. DINGELL. Now, Mr. Nielsen, some insiders have told us that FDA's IT or their information technology system should be scrapped and rebuilt from scratch, simply because it doesn't work. Do you agree with that?

Mr. NIELSEN. No.

Mr. DINGELL. You don't agree?

Mr. NIELSEN. No. I think there are steps. It has to be replaced, but you can't just scrap it.

Mr. DINGELL. OK. We have to have a system, but we have one that doesn't work.

Mr. NIELSEN. That is right.

Mr. DINGELL. And it has got to have major rebuild, does it not?

Mr. NIELSEN. That is correct.

Mr. DINGELL. Now, Mr. England, isn't it true that domestic firms are inspected properly every 2 years because Law requires it? Isn't that so?

Mr. ENGLAND. That is true.

Mr. DINGELL. Mr. England, isn't it true that there is no Law defining frequency of GMP inspections for foreign firms?

Mr. ENGLAND. That is true.

Mr. DINGELL. Shouldn't foreign firms be inspected at least as frequently as U.S. firms?

Mr. ENGLAND. I believe so.

Mr. DINGELL. Isn't it true that foreign drug manufacturers' facilities subject to FDA inspection rarely receive a follow-up GMP inspection?

Mr. ENGLAND. That is true.

Mr. DINGELL. So that means that they are not being adequately inspected, even the small number that are, in fact, being inspected. Is that right?

Mr. ENGLAND. I believe that is true, that there is not——

Mr. DINGELL. Isn't it true that since the year 2000, imported drug volume has nearly doubled but foreign drug program resources have actually declined?

Mr. ENGLAND. That, I believe, is true.

Mr. DINGELL. Now, Mr. Hubbard, isn't it true that today about 2/3 of the drugs consumed in the United States today contain foreign drug components?

Mr. HUBBARD. That apparently is true, yes.

Mr. DINGELL. Of the millions of drug shipments arriving from foreign countries each year, isn't it true that there is almost no chance of an imported drug being sampled, tested at entry into this country?

Mr. HUBBARD. That is correct, Mr. Chairman.

Mr. DINGELL. And if they are sent back out, they can simply be brought in through another port?

Mr. HUBBARD. Unfortunately, that does happen.

Mr. DINGELL. And that happens also with regard to food, although that is not the subject of this hearing?

Mr. HUBBARD. Yes.

Mr. DINGELL. Aren't we buying even larger percentages of our drug ingredients from producers in developing countries overseas with virtually no or no FDA inspection?

Mr. HUBBARD. That is correct.

Mr. DINGELL. Mr. Hubbard, can the FDA ensure the safety of imported drug products at its current rate of foreign inspections?

Mr. HUBBARD. I am sorry, Mr. Chairman. I missed that.

Mr. DINGELL. Can the FDA, and I apologize for that. I had a very serious dental visit this morning. Aren't we buying even—or, I am sorry. Can the Food and Drug assure that the safety of imported drug products is real at its current rate of foreign inspections?

Mr. HUBBARD. Oh, no.

Mr. DINGELL. Given the volume of foreign drug products imported in the United States, isn't the only real way to ensure drug safety and safe drug supply to significantly increase the resources to conduct on-site inspections overseas?

Mr. HUBBARD. I certainly believe that that is the biggest need, yes.

Mr. DINGELL. Now, gentlemen, this panel has over 80 years of FDA experience. Are things worse now than they have been before, or are they better?

Mr. ENGLAND. I think that you would have to say that they are worse now.

Mr. HUBBARD. I think I would have to agree, simply because the globalization has caused us an enormous shift of suppliers from here to developing countries——

Mr. DINGELL. What you are saying is that the risk is higher and the resources are lower? Is that a fair statement?

Mr. HUBBARD. That is correct. And then you have got the concomitant concerns of people buying drugs over the Internet and things like that, so, yes, there are great risks out there.

Mr. DINGELL. Now, why, gentlemen and ladies, are things worse now than they have been before? Starting with Dr. Crosse.

Ms. CROSSE. I think, as we have heard, the globalization of the market and the decrease in the resources that have been available to try to handle that.

Mr. DINGELL. Sir?

Mr. NIELSEN. Also, besides the funding, also the failure to redirect the resources to the global economy condition.

Mr. HUBBARD. The drugs knocking on our door are less safe, so therefore we need more protection, and we have been cutting the FDA, so that, to me, is a simple equation.

Mr. ENGLAND. Yeah, I believe the combination of all those is true. I think there is also a continuing culture that it is just easier for the FDA to think in terms of domestic regulation, because they are used to it, the Statute was built that way, and this NAFTA, the conversions that happened in NAFTA and the economy, just have not carried over into the FDA. They persist, I think, really, on a pre-NAFTA platform rather than a post-NAFTA platform.

Mr. DINGELL. Would this observation be correct? FDA said it has a risk management plan. That risk management plan, being as deficient as it is in personnel, money, and in the way that it works, is actually of no value at all. Is that right?

Mr. ENGLAND. I wouldn't say it is of no value. I would say it has——

Mr. DINGELL. Limited value.

Mr. ENGLAND. —limited value.

Mr. DINGELL. Now, would I be fair in saying that simply assures that perhaps a lesser number of people are going to be killed, defrauded, or hurt by imported pharmaceuticals? Is that a fair statement?

Mr. ENGLAND. I think that would always be true, that if you have less resources assessing risk you always then would have a lower number of people protected by those programs.

Mr. DINGELL. Does the rest of the panel agree? There is no nod button on the recorder's machine here.

Mr. NIELSEN. Absolutely agree.

Mr. DINGELL. Mr. Chairman, I have used more time than I am entitled to. Thank you for your courtesy.

Mr. STUPAK. Thank you, Mr. Dingell. We have three votes on the floor. I think we are going to recess until twelve o'clock. Let us try to get back at twelve o'clock so we can continue.

I am looking down this row. None of you guys can do it in five minutes, I can tell you that right now. Go ahead, Mr. Burgess. I think you were next in the—I was going by your list of attendance, and I think Mr. Burgess—OK, Mr. Walden. I know he will stay at five, and I know Mr. Burgess won't, so why don't you go ahead?

Mr. WALDEN. All right, thank you. Thank you, Mr. Chairman. My colleague from Pennsylvania, Mr. Murphy, suggested this question, and I think it is a really good one, and I would like a yes or no answer out of each of the panel members. If your child were prescribed a drug that you knew was manufactured in a facility in China that is not inspected, would you let your child take your drug? Dr. Crosse? Yes or no?

Ms. CROSSE. Yes, because if they were ill enough to require a prescribed drug, I would be concerned that they take something.

Mr. WALDEN. Mr. Nielsen?

Mr. NIELSEN. Yes, because I don't feel there is an option.

Mr. WALDEN. Mr. Hubbard?

Mr. HUBBARD. I think we are doing it every day, so there is no choice.

Mr. ENGLAND. I would agree. It is what you are left with, that you have nothing else to go to.

Mr. WALDEN. That is a pretty sad commentary, isn't it? That we are putting our kids' health at risk to take drugs that a physician prescribes that we all now know are coming from factories that we don't have the resources to inspect. That is a scary proposition when we know our toothpaste is poisoned. We know our dog food got poisoned. We know—and we have no options? Then we had better change how FDA operates. Mr. England, I want to ask you a couple of questions here. Please refer to the document from the FDA's Web site called "Consumer Update: Ensuring the Safety of Imported Products—Q&A with Deborah Ralston, Director, FDA's Office of Regional Operations". According to the FDA questioner, the number of imported goods that FDA regulates has more than doubled in the last 5 years. Ms. Ralston states on the Web site that the FDA has a team of more than 2,000 scientifically-trained spe-

cialists who conduct inspections, analyze samples, and monitor the entry of regulated products at our nation's borders. Is this number of 2,000 FDA people working on imports a credible number?

Mr. ENGLAND. I have no idea who they could be. I would think that roughly 200, maybe between 200 and 250, in the inspection side, perhaps another 100 in the lab side, that spend more than 50 percent of their time, probably is a more reasonable number.

Mr. WALDEN. Ms. Ralston states that the FDA analyzes about 30,000 import product samples annually. That sounds like a big number, doesn't it?

Mr. ENGLAND. Sure does.

Mr. WALDEN. 30,000 import samples.

Mr. ENGLAND. It does sound like a big number.

Mr. WALDEN. This 30,000 samples is out of how many lines of entry?

Mr. ENGLAND. 18 million, probably, this year.

Mr. WALDEN. So 30,000 out of 18 million. Do you think that is an acceptable number when our nation's health relies on these drugs?

Mr. ENGLAND. It is a remarkably small percentage.

Mr. WALDEN. Do we know what kind of product samples she is talking about? Do you think a lot of these samples are drug products?

Mr. ENGLAND. The majority would be food, I would expect.

Mr. WALDEN. So the majority of the 30,000 of the 18 million would be food samples.

Mr. ENGLAND. I would expect that, yes.

Mr. HUBBARD. Yes, they sample about 20,000 foods each year, so the majority are food.

Mr. WALDEN. So we are down to 10,000? I was a journalism major, not a math major, but that only leaves about 10,000, then, that you estimate would be drug samples, out of 18 million?

Mr. ENGLAND. It could be cosmetics, and then it could be some pharmaceuticals.

Mr. WALDEN. Do these analyses tell the FDA how many of the samples analyzed were safe?

Mr. ENGLAND. Well, the FDA would have. They would make a determination on the given shipments that they are analyzing, but it doesn't tell them anything about the next shipment.

Mr. WALDEN. Do these analyses of these product samples generate an FDA report of any kind?

Mr. ENGLAND. My understanding is that there may be some information inside the system, but it is probably very difficult, if not impossible, to retrieve it from the system, so I would guess probably no.

Mr. WALDEN. Would you expect that the committee would be able to obtain from the FDA the results of these sample analyses, what the FDA learned, and what action the FDA took?

Mr. ENGLAND. I would expect that they should be able to do that through its fax system and the OASIS system, the combination of those two systems. Mr. Nielsen actually may know better.

Mr. WALDEN. Mr. Nielsen?

Mr. NIELSEN. Yes, I think they should be able to provide that.

Mr. WALDEN. So you could provide it to us, but it sounds like no report is generated internally at the FDA for the FDA's own use, do you think?

Mr. NIELSEN. It is usually case by case.

Mr. WALDEN. All right. Ms. Ralston states the FDA conducted approximately 30 inspections of manufacturing processing sites in China for FDA-regulated products. How many establishments are there in China involved with FDA-regulated products?

Mr. ENGLAND. Wow——

Mr. WALDEN. Wow?

Mr. ENGLAND. It is a very large number. I don't know the answer. I know that Dr. Lumpkin testified, I think a couple weeks ago, that there were 3,000 medical device manufacturers alone in China. That is just that industry, which probably is a fraction of the entire——

Mr. WALDEN. Does 30 inspections a year sound like an adequate number to ensure the safety of products from China?

Mr. ENGLAND. Not overall of products from China, no.

Mr. WALDEN. All right. My time has expired. I thank Mr. Chairman.

Mr. HUBBARD. Mr. Chairman, may I make one comment to Mr. Walden's earlier question?

Mr. STUPAK. Yes, sir.

Mr. HUBBARD. I don't think we should leave people with the impression, though, that our drug supply is unsafe.

Mr. WALDEN. It is just vulnerable.

Mr. HUBBARD. It is vulnerable, exactly. I mean, I think, you know, the manufacturers here that receive these foreign components do a good job, under FDA supervision, to screen them. So we are not, like, taking dangerous drugs every day. But, as you said, we are vulnerable.

Mr. STUPAK. But 80 percent of the active pharmaceutical ingredients found in over-the-counter and prescription drugs are from offshore.

Mr. HUBBARD. Right. And so clearly there is a risk, but personally I don't think the drug supply in the United States—I think it is actually the best in the world.

Mr. STUPAK. Right, and in their—I don't mean to argue or take any more time, but we inspect 97 percent of the plants here in the United States every 2 years. They do a good job domestically, but offshore is where the problem is occurring. If 80 percent of your product is coming from offshore, we have to devote the resources to offshore.

Mr. HUBBARD. OK. The manufacturers here are required, under FDA supervision, to do lots of screening before that pill actually goes to the drug store, so——

Mr. WALDEN. My concern is it is only a matter of time if we don't fix the inspection process.

Mr. STUPAK. Absolutely.

Mr. HUBBARD. No, I don't disagree with you at all.

Mr. WALDEN. Mr. Chairman, could we put that document in the record? I ask unanimous consent.

Mr. STUPAK. Yes. Without objection, the U.S. Food and Drug Administration interview, Question and Answer with Deborah Ralston, will be entered as part of the record.

With that, we have 3½ before we have a vote time expires. We will be in recess. Let us still shoot for 12 o'clock, shortly after twelve o'clock. We will continue. We still have many members that would like to ask questions of this panel. Thank you.

[Recess.]

Mr. STUPAK. If am I may ask Mr. Nielsen, Mr. Hubbard, and England, Mr. Dingell and myself, Mr. Pallone has put in legislation which would generate about $300 million for drug safety, drug inspections. Have any of you had a chance to review that legislation, Mr. Nielsen, Mr. Hubbard, or Mr. England?

Mr. HUBBARD. Is that the user fee?

Mr. STUPAK. Right. The user fee with the Food and Drug bill we put in.

Mr. ENGLAND. I have reviewed it.

Mr. NIELSEN. Yes.

Mr. HUBBARD. Yes.

Mr. STUPAK. Any comments on it?

Mr. NIELSEN. I fundamentally have difficulty with a user fee for that purpose. I just don't see—I use a parallel of perhaps if I had to pay a user fee for IRS to process my income tax form, they came to audit me, and I had to pay them to audit, and then they put me in jail and I have to pay for that, too. And, on the other hand——

Mr. STUPAK. That is not the way it goes, though.

Mr. NIELSEN. What is that?

Mr. STUPAK. Nothing.

Mr. NIELSEN. Yes. But I do think it needs to be considered——

Mr. STUPAK. But where else would you go to look for the resources? I mean, you need a significant amount of resources. Obviously, the FDA has been reluctant to ask for it. We generate $300 million. That is $1000 a line. That is all it is, a line. A line will give you a boat-load of goods, or it can be one box of goods. But——

Mr. NIELSEN. Well, the problem I see with that is, FDA can ramp up the foreign inspections. If everything is done as it is done now, you are still not going to deliver that information into the import process. You must have the IT, and I believe a user fee, a nominal, like 50 cents or $1.50 per line user fee could be justified in providing service and the infrastructure to do what needs to be done.

Mr. STUPAK. So, in other words, if we did leave it at that $1000, let us say, we have got to dedicate at least part of that for IT, because without a data system we are done.

Mr. ENGLAND. That is right.

Mr. HUBBARD. If I——

Mr. STUPAK. Go ahead. Mr. Hubbard?

Mr. HUBBARD. The problem I have seen with user fees, Mr. Chairman, is that the budgeters of the world see new money come in the FDA, so they cut the budget in the non-user-fee areas, and that clearly happened with the PDUFA program, so the food program and the import programs have actually gotten weaker. FDA has lost about 1,000 people in the last decade from appropriated dollars, even though the agency's total budget has gone up, due to

these user fees. But the user fee money is dedicated only to the review of new drug and device applications.

Mr. STUPAK. Correct.

Mr. HUBBARD. So you have actually had a shift where some programs are getting richer, and others are getting poorer. And so I think you have to find a way to make sure that the budget folks don't essentially take that money away from appropriations——

Mr. STUPAK. And then substitute it for annual——

Mr. HUBBARD. Exactly. That is what happened with user fee, and that is what happened with the earlier user fees, and so you have to build some sort of firewall.

Mr. STUPAK. OK. Mr. England?

Mr. ENGLAND. I would say that the way I read the user-fee legislation is that those monies would be used to essentially help pay for border examinations and samplings of imported product. I am afraid that it reinforces a finished product testing regime. I also——

Mr. STUPAK. Would you say it does not work, or is not the preferred method of protection, finished product hitting the——

Mr. ENGLAND. That is correct. And the end result——

Mr. STUPAK. Do you want to explain this?

Mr. ENGLAND. The end result is you are paying for a program that is not really useful if you don't know the GMP status of the manufacturer. I mean, if you were to test within the same batch of drug, that batch, depending upon its size, could be different at the front end of the process from the back end of the process if GMPs are not in place. So if you happen to sample from one portion of that, you may not even be able to detect a problem within the same batch. So I think finished product testing of drugs in particular is troublesome, but, and I agree with Mr. Nielsen's idea of funding the IT program perhaps through user fees at the border level. I think another aspect about it is that if you take that money and then put it into GMP inspections in the foreign facilities, now you have the U.S. importer paying for essentially inspections by the FDA in the foreign market and getting free quality assurance advice from FDA, and who knows how many times they have to go back before they get it right? So I think perhaps you could do it on the registration end of it, and that way you have some gate, and people wouldn't be inclined to go on and just register their facilities if they knew that there was money that was involved in it, a. And b., that that money could be used to fund the FDA conducting an inspection in their facility.

Mr. STUPAK. Good point. Ms. DeGette, for questions? I believe you have eight minutes, since you waived your opening.

Ms. DEGETTE. Thank you. Thank you, Mr. Chairman. Well, all of you testified that the FDA needs increased resources to inspect these foreign facilities, and I certainly agree with that, but I don't think it is just an issue of resources because you also testified that the current computer—I think Dr. Crosse in particular testified that the current computer systems are inadequate for cross-referencing and determining the various facilities abroad, so I am wondering if you can comment, how much of the problem is more resources, and how much of it is an inadequate computer system, and what can we do to get the FDA to update their computers?

Ms. CROSSE. Well, I think it is both. I think part of the resource issue is resources to update their information technology systems and that the resources have not been devoted to that, and there was some testimony about plans that they had had that were scrapped, largely because of the lack of resources.

Ms. DEGETTE. But do you think there is a commitment on the FDA's part to—a recognition that their IT systems are inadequate and a commitment to improving those systems?

Ms. CROSSE. I believe that there is a recognition that their systems are inadequate. I think that the question is better asked of others, whether there is a commitment.

Ms. DEGETTE. All right. Let us hear from Mr. Hubbard.

Mr. HUBBARD. I would say that I saw the import folks and the regional affairs folks ask for funding over and over again through the budget process for these systems, going all the way back to your hearings of the 1980's, and that money was always denied. And even the current administration, they had this theory that too many IT resources were being wasted, and FDA was being constantly squeezed on IT, when IT actually saves you money in the end.

Ms. DEGETTE. Right.

Mr. HUBBARD. I hope that Dr. von Eschenbach will describe how he is committed to fixing that system now, but money is clearly the reason that they don't have it now, in my view.

Ms. DEGETTE. Well, another thing that we could do with money, aside from improving the IT systems, is improve the system of inspection that we have. Dr. Crosse testified, and she briefed us yesterday on this pathetic system that they have for actually inspecting the overseas facilities, where they take a volunteer, and the volunteer goes into this factory, and then the volunteer doesn't even have a translator. I can't imagine how you could get any adequate information inspecting a facility when you didn't even have someone to translate for you, especially if it is a foreign facility that has a vested interest in not providing and willfully withholding information. I am wondering if you can comment a little further on that, Dr. Crosse.

Ms. CROSSE. Well, we certainly think that is a concern. When they have a need for translation services, they are, in general, relying upon a representative of that establishment to do the translation for them. I have talked with some of the folks from FDA's Office of Regulatory Affairs, and they indicated that they believe there are many items they can look at. They can still physically inspect the plant and see if whether there are, you know, leaking pipes and other sorts of problems, that some of the data they need to review is numeric, but some of the data they need to review is not numeric, and some of what they need to obtain has to be gathered through interviews and discussions with officials there in the facility. And so——

Ms. DEGETTE. And then they are relying on——

Ms. CROSSE. I have a concern.

Ms. DEGETTE. And they are relying on translation by representatives of the officials at the facility.

Ms. CROSSE. That is right, and they are relying on that facility having an understanding of what is expected out of our regulatory system.

Ms. DEGETTE. And counsel just told me he was in a factory in China, and they wanted to talk to some of the employees, and the State Department representative who was with them said, you know what, what the translator is saying these people are saying, they are not saying. And you would have no way to know that if you were just some FDA inspector standing there, right?

Ms. CROSSE. Correct.

Ms. DEGETTE. And that is a place where resources might help. Does the FDA, in your opinion, acknowledge this problem as well?

Ms. CROSSE. They have been reluctant to acknowledge this as a problem to us.

Ms. DEGETTE. Does anyone else have a comment on the whole inspection process and how it can be improved, Mr. England?

Mr. ENGLAND. I would just note, and actually a number of days ago I was on the phone with somebody in the FDA, and that happens to be one of the foreign inspection cadre participants who has done inspections quite a number of years for FDA as a foreign inspector, and recounting, you know, they have a short period of time to get in-country and maybe a long trip. They are tired when they get there. They have a couple of days to do an announced inspection, maybe 2 or 3 days, which, that same inspection, if there are problems identified, which there probably will be, in a foreign inspection, would probably have been stretched out to 10 to maybe 14 days, and then they have to get on the train or plane, get the next one. By the end of several weeks, now they are going back to their notes and trying to remember and rebuild the inspection and do their inspection reports. I mean, I think all of those kinds of things, those add to the complexity of just even the current system at FDA. Add translation, add the fact that the volunteers are doing it, that it is announced. Many times the inspector is relying on the inspected firm for transportation between locations.

Ms. DEGETTE. Great. Now, when the FDA inspects domestic facilities, it can arrive unannounced, it has more enforcement ability over domestic than foreign countries, and it doesn't have to have things translated, and I am wondering if we need to beef up our foreign inspections, realizing that these are all impediments. Dr. Crosse? Or, Mr. Nielsen?

Mr. NIELSEN. I think that is very—I mean, there has to be a credible presence in the industry to give the incentive to comply, for those provisions that do result in safe products. There has to be a credible presence.

Ms. DEGETTE. And one last question, to Dr. Crosse's point, the GAO findings are that the current U.S. firms are inspected every 2 years by the FDA, correct?

Ms. CROSSE. The data that they provided to us show that they actually get there about every 2.7 years.

Ms. DEGETTE. And there is no Law defining the time between inspections for foreign firms and, in fact, at the foreign firm inspection, because of FDA's reliance on volunteers and so on, it is much more sporadic than domestic. Is that right?

Ms. CROSSE. That is correct.

Ms. DEGETTE. So I would think it would make sense to require that foreign firms shipping drugs to the U.S. be inspected at least as frequently as U.S. firms. Would you not agree with that, Dr. Crosse?

Ms. CROSSE. I think there is certainly every reason to believe that the risks abroad are the same or greater than the risks in domestic establishments.

Ms. DEGETTE. Would the rest of you agree that we should have at least the same type of inspection system we have for domestic firms, Mr. Hubbard?

Mr. HUBBARD. Well, I think it would be meaningless without the resources. They can't do the current statutory requirement of every 2 years. If you impose that on them for foreign, they would simply fail, so you would have to have some sort of provision to make sure that they have the resources.

Ms. DEGETTE. Well, obviously, you can't do the inspections without the resources, but don't you think that we need to have some kind of a standard for the foreign inspections, especially in light of the recent revelations that we have had from China and other countries? I mean, we are not even talking here about drug counterfeiting. We are not talking about drug re-importation from the Internet. We are talking about legitimate drug ingredients that are used for FDA-approved drugs, and we are not even able to inspect them because we don't have the resources to inspect them like we do domestically. That seems like a backwards system, that we should really be focusing on the foreign producers and obviously domestic, too, but it seems like we shouldn't say, well, we are not going to inspect foreign because we don't have the resources.

Mr. HUBBARD. Well, you are absolutely right. It is indefensible that we would be doing the domestic firms so frequently and the foreign firms so infrequently, but again, FDA has got to be given the wherewithal to actually do that.

Ms. DEGETTE. And do you think they have the will to do it if we gave them the wherewithal?

Mr. HUBBARD. I would certainly hope so.

Ms. DEGETTE. Mr. England?

Mr. ENGLAND. I would note that in the worst-case scenario, the equivalency is made between the domestic and the foreign industry as far as the frequency of inspection, without resources. What that would at least force is a shifting of existing resources towards risk. It really should force a risk assessment with regard to foreign versus domestic, because in these foreign manufacturers, many times these countries are developing countries. They don't have a regulatory regime, like we have in the United States. They may not have potable water, at least in the community. Hygiene could be deficient. So I think the risks, if you were to actually lay them side by side, the risks would be greater in the foreign market. I think it would at least force that shift into the foreign market.

Ms. DEGETTE. Thank you. The Chairman was right. This was a wonderful panel, one of the best I have seen in my years in Congress. Thank you for your testimony.

Mr. STUPAK. Mr. Burgess, for questions.

Mr. BURGESS. Thank you, Mr. Chairman. Dr. Crosse, in your testimony, and forgive me for being out of the room. So if this has

been asked, I apologize. On the use of translators, how big a deal is that?

Ms. CROSSE. I think in some countries it has got to be an enormous deal.

Mr. BURGESS. Is there a risk that, since we are depending upon the company, the manufacturer, to provide the translator, that it could be an inside job or an inside plant?

Ms. CROSSE. There certainly is that risk. That is a concern that we would have.

Mr. BURGESS. Are those interviews or exchanges that are taking place between the FDA and the manufacturer through a manufacturer's supplied intermediary, are those taped or transcribed? Is there any way to quality check the quality of the information that has been given back and forth? Because even with someone's best of intentions, just in the translation, as we all know, things can get lost.

Ms. CROSSE. Not to my knowledge. No, I don't believe so.

Mr. BURGESS. On the whole issue of the database, I guess, Mr. England, this morning downtown former FDA Commissioner Mark McClellan was addressing this issue, more from the standpoint of how it interacts with, do we get the most efficient technology, do we deliver the most value for the patient, and the previous lack of a reliable database at the FDA, in this country, for those types of activities, made that a real problem. I think it was referred to as stove-piping. I had a younger staffer who didn't know what a stove pipe was, so maybe we had better use silo. I guess they know what a silo is, maybe not from farm country. But Dr. McClellan was talking about the coverage side low, the technology side low, and how we needed to be able to bridge that gap, and it sounds like we are kind of talking about the same phenomenon here. Is that correct?

Mr. ENGLAND. I think it is true that the IT systems FDA has are siloed, and they are really wrapped around the agency's internal siloing.

Mr. BURGESS. And yet in the private sector, because we also heard testimony from—or, not testimony, but it was a symposium downtown with Health Affairs for their 25th anniversary, I think it was Mr. Williams from Aetna Insurance Company. It seems like I heard 10 years ago that they reinvested about 10 percent of their capital into health information technology or information technology, and this morning he gave a figure of 15 percent of his work force of 34,000 people across the country. Most of them aren't out there selling insurance and doing customer service. 15 percent are actually involved with development of software, maintaining their infrastructure, and I think he made the statement, I may be misquoting, but I think I heard him say that if Aetna's information technology department were a stand-alone company it would be one of the largest software development companies in the United States. So it just goes to underscore how much private industry in this country has recognized that they must invest in this, and it sounds like, even though we did make some big steps in the FDA reauthorization bill as far as monitoring the treatment database, we have got to do a lot more as far as certainly this aspect of it, in monitoring foreign manufacturers. Is that a fair assessment?

Mr. ENGLAND. I do think it is fair. I would even add that I think because of those kinds of investments in the private sector, and particularly in the areas where FDA has jurisdiction, and the risks maybe even perceived with some relevance between what FDA is trying to do and what maybe, for instance, Aetna might be trying to do, there are more off-the-shelf technology that you can take and you can modify rather than developing systems from scratch. I mean, the OASIS system essentially is a from-scratch software development program. There are some off-the-shelf elements to it, but that ends up costing a fair amount of money, to try to develop it and then maintain it. Then you become married to a contractor as well, which is problematic.

Mr. BURGESS. And what would be some examples of that, in the private sector currently?

Mr. ENGLAND. Examples of off-the-shelf technology? Well, I mean——

Mr. BURGESS. What companies are, say, doing that in the private sector that are doing it well, that have maybe a similar problem that the FDA has?

Mr. ENGLAND. You would probably see most of it in the Customs international transactional environment, and you would see it in—that is why I don't want to misidentify any specific companies——

Mr. BURGESS. Right.

Mr. ENGLAND. But you also would see it in the defense area, where you have just got many, many transactions, risk that is built into those transactions someplace, and the ability to process a high volume, high, fast stream of data, in order to think about that data, in order to assess and mitigate risk.

Because we will never be able to eliminate that risk, but we ought to be able to manage it a little bit better than we are doing. Now, I get the impression from talking to the panel that this—I think, Mr. Hubbard, you said 1986 was the earliest figure I heard, but 1998, the year 2000, I mean, this has been something that we have all been aware of, and I am a recent arrival, but people have been aware of for some time, so through several administrations, both Republican and Democratic, through several Congresses, both Republican and Democratic, so this obviously doesn't become a partisan issue or an issue that is isolated to one administration, but I would just ask, since there is so much familiarity with it over time, what—we have a relatively new FDA Commissioner, Dr. Crosse, have you spent time talking to Dr. von Eschenbach about this?

Ms. CROSSE. I have not.

Mr. BURGESS. OK. Mr. Nielsen, what sort of interplay have you and Dr. von Eschenbach had on this issue? Have you brought this to his attention and some of the previous suggestions that were out there, from 2000?

Mr. NIELSEN. No, I have not.

Mr. BURGESS. OK. And, Mr. Hubbard?

Mr. HUBBARD. I was trying to describe how the Commissioner is juggling so many priorities, and when there is not funding to deal with them effectively, some things fall away, and I think imports has been one, historically, that has not been able to rise to the top

for funding. Perhaps, as a result of some of your work this year, that will change.

Mr. BURGESS. And, Mr. England, have you talked with Dr. von Eschenbach about this?

Mr. ENGLAND. I had the pleasure of meeting him for the first time today.

Mr. BURGESS. Well, he is right behind you, so I urge you to get his card and do talk to him about this, because it is clearly important, and clearly, legislation is going to be developed, not from this subcommittee, but out of our full committee, and it is important that we get it right on just so many levels, the safety level now and how we monitor and maintain the system decades into the future. So I yield back, Mr. Chairman.

Mr. STUPAK. Well, thanks, Mr. Burgess. Now you see why it is so important to have Dr. von Eschenbach for all these panels that they can direct——

Mr. BURGESS. But I was trying to make sure we make good use of his time——

Mr. STUPAK. As you were saying earlier this morning——

Mr. BURGESS. This morning, and I wanted to draw that in.

Mr. STUPAK. Mr. Whitfield, questions? I am going to ask a few more, and if you want to go back to the mike, we will go back for a couple more questions. If I may, Mr. England, you talked about, I think it was page 19 of your testimony, about the Bioterrorism Act that we passed, I think it was in about 2002, and it came out of this committee, I know that, and you mentioned food, but we don't have drug imports in there? And that should be amended?

Mr. ENGLAND. The provision that I was speaking about is a provision that requires the agency to design and implement information technology systems related to imported food that will assist the agency in allocating its resources where the greatest risk of, in that case, intentional adulteration of food. But one of the elements there, also, was to facilitate the importation of food that is in compliance with the Act, and I perceive that as being really the opposite side of the risk coin. There is a tremendous amount of product that is out there that is safe. The difficulty is knowing which is which. I mean, to go to the issue of the fact that the domestic manufacturers do screening, that is true, but that is different than saying that therefore we are safe. And so the opposite side of the risk coin is that where industry can demonstrate that they are in compliance with GMPs in the case of the drug industry, that product should be facilitated. That provision, though, is restricted to imported foods. It doesn't cover drugs, devices, or any other commodities regulated by FDA.

Mr. STUPAK. In questions of Mr. Walden, based on this newsletter from U.S. Food and Drug Administration, FDA, on Ensuring the Safety of Imported Products, we were kicking around the numbers. It was 30,000 out of 18 million that they look at each other, and I think you said it was about 10 percent related to drugs, so even if you gave the figure of 30,000 to use, FDA analyzes about 30,000 import product samples annually. Even at 10 percent, or 1.8 million, that is only like two percent, if my math is correct, 30,000 into 1.8 million. That is only, like, about two percent, then, correct?

Mr. ENGLAND. Well, 20,000 of that 30,000 would be foods, so you are really talking about 10,000 out of 1.8 million.

Mr. STUPAK. So it is probably——

Mr. ENGLAND. We are assuming the balance are all drugs, which I don't think they would be. They would be biologics and other products.

Mr. NIELSEN. And, Mr. Chairman, I would expect the majority of those drug samples to be from activities at the international mail facilities.

Mr. STUPAK. So the figure might be closer to 20 percent of one percent of drugs.

Mr. ENGLAND. You are beyond me in your math.

Mr. STUPAK. I am beyond myself, too. That is why I am asking you.

Mr. ENGLAND. I think to Mr. Nielsen's point, though, there also is that, let us say for the sake of discussion that it is 5,000 to 7,000 of the—30,000. Probably a large percentage of those are inspections conducted by folks at FedEx or UPS or an international——

Mr. STUPAK. For Customs, or whatever it may be.

Mr. ENGLAND. Looking at very, very small packages that Customs happens to kick out. In other words, not 30 metric tons of product coming in. Probably a good percentage of even the drug inspections would be related to that.

Mr. STUPAK. But then it gets to the point I was trying to make. If it is only one percent of the food that we are inspecting, drugs are far less than that one percent, then, of the drugs coming in here, so it is a problem, not just against drugs from foreign countries, but also food, drugs. I mean, we got a serious problem here. And it seems to lie with the databases, at least that is where we should start. Mr. Nielsen, there is a new program. Can you explain a little bit? I think it is called Predict, that is used for seafood? And that got funded through an earmark, correct?

Mr. NIELSEN. Yes.

Mr. STUPAK. A congressional earmark that everyone is against right now but this was an earmark that was actually put in. That is how it got funded at the FDA. Can you explain this a little bit more to me? How would it relate here to drugs?

Mr. NIELSEN. Yes, and it actually also falls into some of the low-hanging fruit of the ISP that was implemented. But the Predict model is being piloted or at least was being piloted, I believe in Los Angeles, for the seafood industry. I was program manager for the development while I was Director of Import Ops, which is why I know about it. But what it really does is it starts to integrate information from both external and internal sources. It actually learns the risk posed for imports based on a variety of data points and will assist the entry reviewer in deciding which of the riskier shipments to do the examinations.

Mr. STUPAK. Thank you. Mr. Burgess, do you have any further questions before we let this panel go?

Mr. BURGESS. Yes, I do, Mr. Chairman. Thank you for coming back to me. Just to follow up on my last thought before we got cut off, I mean, we have all been fairly intense in our criticism of the FDA, which is fair. The Commissioner of the FDA has been in his position since December of last year, so not quite a year. Mr. Hub-

bard has already correctly alluded to the fact that there is lots of things going on at the FDA, lots of different things to juggle, so it is fair to criticize the FDA, but at the same time if we have got constructive solutions, and it sounds like we have had those, at least been thinking about those for at least 20 years, so, I mean, again, I just concur it was a great panel, but I encourage you to follow up with Dr. von Eschenbach, and let us talk about these and explore them. Don't, you know, don't leave it to us to write the Law by, you know, a vacuum, because I don't think we will do a very good job. So we count on your input, and we count on that input being delivered to Dr. von Eschenbach, so in turn the agency can help us help the agency. Now, on the issue, Mr. Hubbard, you mentioned human tissue at one point, I think, in your discussions. Is that correct?

Mr. HUBBARD. Right. Well, that is just one of many, many things that have popped up in recent years that needed attention, got some, but then drifted away.

Mr. BURGESS. Well, it got my attention when you said it, because obviously there have been some fairly disturbing, even macabre, stories in the news in this country about some practices with dealing with human tissue that I found very disturbing. Are we importing human tissue products from overseas?

Mr. HUBBARD. When I was in it, there was some. We did a sting in which a Romanian gentleman was selling us the body of a Russian gentleman who had apparently died in the street, and he died of AIDS, and he was selling his whole body to us and shipping it via the airlines flight that day. So, I mean, it was that kind of example that caused the Commission at that time to put in place some rulemaking and beef up regulation. The problem is, the funding was never there, in my opinion, to really have a permanent program to inspect tissue banks to make sure they were following proper procedures.

Mr. BURGESS. Is that likely to still be continuing today, as we have seen this advance in globalization and all the other pressure put on the drugs, the toys, the food imports? Is it likely to be additional pressure put on——

Mr. HUBBARD. I don't know exactly what is going on out there now, but I can't imagine the FDA has sufficient resources to adequately inspect all of that industry.

Mr. BURGESS. Well, Mr. Chairman, I know that is beyond the scope of this hearing, but I would encourage this committee to very seriously consider—for some time I have thought that we ought to look at the use of human tissue that originates in this country. I had no idea, no idea that there was the possibility that there is human tissue coming from outside. And Mr. Hubbard correctly alluded to some of the problems there, and if there is lack of quality in the active ingredients in a Lipitor pill, goodness knows, we want that quality assurance for people who are going to have human tissue grafted or implanted. One last thing, Mr. Nielsen, on the good manufacturing practice, it seems like that would affect the whole debate of re-importation. That is, if we want good manufacturing process, and we are crying out for more inspections and more funding for the FDA to do more inspections and move that chart graph that we saw, so that that blue area becomes as a greater and great-

er footprint, but then we have people in Congress today who are arguing for, hey, we can get cheaper drugs if we just allow re-importation from Canada, and of course the supply chain then comes from who knows where, so it almost seems as cross purposes to argue for improvement of good manufacturing processes and at the same time argue for re-importation Laws. Am I missing something?

Mr. NIELSEN. If the two are not connected, absolutely.

Mr. BURGESS. Well, just by definition, or at least the legislation I have seen offered for re-importation, it doesn't really seem to have a lot of control. It just says, from Canada, and we have all seen the reports that what looks like a maple leaf might in fact be an insignia of some other country and, as someone said, from the darkest corners of the world. So if we embrace re-importation wholeheartedly, again, as some people have suggested, and that is a bipartisan issue. I am not putting that in anyone's theme in particular, but we know who has been arguing for that pretty forcefully for some time, basically that ends all product testing, does it not?

Mr. NIELSEN. Yes, and I have to say, on the GMP, the principle of the GMP is it is going to prevent the entry—it is really going to contribute, but it is the whole process, from the application process for the prescription drugs, to the post-surveillance process, including adherence to the GMPs. If you don't have the whole picture, you are just adding risk to it, and I have to give an example. This is not just a finished drug issue. The industry that is overseas are also finished product manufacturers. There is even less oversight of the ingredients going into the finished products overseas. At least here, when the APIs or the ingredients come in, it is not going to a black hole. We know where it is going. It can be checked. There is a warehouse. There is a facility to go to, and there is a process for checking potency, identity, and certificates of analysis, and it is not an issue of waiting for more bodies to show up. The med watch, the adverse events are not necessarily going to say everything is going to be OK unless there is an adverse report here. The carbamazepine scenario experience that I painted in my written testimony is a good example where the products going into the formulation have a potential adverse effect if it is not in compliance with both the application and the GMPs governing that manufacturing process. The good thing about the carbamazepine is if it didn't work, carbamazepine is an anti-convulsant drug. If it didn't work, the epileptics were seizing. You could see it.

Mr. BURGESS. So the bio-assay was positive.

Mr. NIELSEN. On the other hand, if a drug, like gentamycin, is knocking your kidneys out, you are not necessarily going to see it. And you are not necessarily going to know that it is not doing what it is supposed to do. I believe generally the public, all of us, have kind of been trained, if something doesn't work, something is wrong in my metabolism that caused that drug not to work. Well, maybe yes, maybe no. And what we are trying to do is say that there is a way to minimize the risk from that drug that is supposed to help you.

Mr. BURGESS. I thank you for that. It was very illuminating. Mr. Chairman, I do just need to mention, I think I mentioned a drug by brand name, and I was using that only for the purposes of illus-

tration. I have no knowledge that that drug of that brand name even is manufactured in China. So I apologize for that oversight. I was simply trying to make a point, and I yield back.

Mr. STUPAK. You have an 80 percent chance of being correct. Dr. Crosse, thank you, and thank you to your staff for pulling everything together quickly. I know you are going to continue your work, and this committee and subcommittee appreciate it. To our panel, thank you very much. Both sides, everyone has been saying what a great panel. We could go round and round on questions, but we do have two other panels. But thank you for your time. Your 80 years of experience with the FDA certainly helped us out here today. Thank you very much. I will dismiss this panel, and we will move to our second panel of witnesses.

Mr. John Dubeck, the partner in the law firm of Keller and Heckman, as well as counsel to the Bulk Pharmaceutical Taskforce at the Synthetic Organic Chemical Manufacturers Association; Mr. Bruce Downey, chairman and CEO of Barr Pharmaceuticals and chairman of the Generic Pharmaceutical Association; and Mr. Guido Villax, the immediate past chairman of the Pharmaceuticals Business Committee and member of the Board of Directors of the European Fine Chemicals Group. Gentlemen, would you all come forward? It is the policy of this subcommittee to take all testimony under oath. Please be advised that the witnesses have the right under rules of the House to be advised by counsel during their testimony. Do any of you wish to be accompanied by counsel? All witnesses indicate no, so I ask you, raise your right hand, take the oath, please.

[Witnesses sworn.]

Mr. STUPAK. Let the record reflect the witnesses answered in the affirmative. They are now under oath.

Mr. Dubeck, we will begin with you, with your 5-minute opening statement, please, sir.

TESTIMONY OF JOHN DUBECK, PARTNER, KELLER AND HECKMAN, LLP, AND COUNSEL, BULK PHARMACEUTICAL TASKFORCE, SYNTHETIC ORGANIC CHEMICAL MANUFACTURERS ASSOCIATION

Mr. DUBECK. Mr. Chairman, and members of the subcommittee, on behalf of the Bulk Pharmaceutical Taskforce and the Synthetic Organic Chemical Manufacturers Association, SOCMA, I thank you for this opportunity to testify on two key points. First, the current system for regulating imported drugs is putting American consumers' health and safety at risk. Second, there is a solution; more frequent and in-depth inspection of the foreign facilities making these drugs.

The Bulk Pharmaceutical Taskforce submitted a citizens' petition to FDA in January of last year, outlining the risks associated with imported drugs and providing suggested solutions. These risks have been well highlighted already, and I will not repeat them. We are disappointed that we have received no substantive response from the agency.

The drug manufacturing industry today is structured vastly different than it was 30, 20, or even 10 years ago. No longer are drugs primarily manufactured in-house by the major pharmaceutical

companies. Rather, these companies have increasingly turned to outsourcing their ingredients and sometimes even the finished product. The suppliers of these outsourced products are overwhelmingly foreign manufacturers. FDA is required to inspect domestic drug establishments every 2 years. These inspections are unannounced, and a single inspection can extend over many weeks and may involve many separate visits. And I might add that on subsequent visits at a given inspection an inspector may call in other experts in specialties to assist in observing something that is seen during the first part of an inspection.

This is no comparable obligation on FDA to inspect foreign facilities. Since FDA must be invited to perform its official duties on foreign soil, a foreign facility always receives several weeks' notice of an impending inspection, and the length of the inspection is typically driven by travel schedules, rather than the compliance status of the facility, and it is impossible to bring additional expert investigations to review specific issues. As a practical matter, a foreign manufacturer is unlikely to be inspected for cGMP compliance, except in the context of a pre-approval inspection. If you wish, I can explain later the difference between pre-approval inspections and cGMP inspections and why the former is of little value in assuring the ongoing quality and purity of imported drugs.

If routine cGMP inspections are unlikely to occur, it is very tempting for management to put a low priority on maintaining cGMP compliance. Statistics presented at a cGMP conference in 2005 indicate that cGMP inspections of foreign firms result in significantly more violations than seen in domestic firms. When comparing data solely from pre-approval inspections, the same discrepancy is seen. Deviations from cGMP were more serious in foreign facilities than in U.S. facilities. These numbers cry out for FDA to conduct more frequent inspections of foreign facilities. They also underscore that the frequency of foreign cGMP inspections is so low that managers of foreign facilities have apparently made the business decision to spend less time, attention, and money on ensuring that their drug manufacturing operations comply with cGMP than is necessary to assure compliance.

A dramatic and drastic overhaul of FDA's approach to the risk posed by foreign manufactured drugs is long overdue. The manufacturing side of the pharmaceutical industry has changed substantially, and yet FDA's allocation of inspection resources remains unchanged from an earlier era. In order for FDA to give cGMP inspections of foreign facilities the priority it deserves, the Bulk Pharmaceutical Taskforce proposed that FDA do three things. FDA should abandon its policy of prioritizing domestic and foreign facilities separately for inspection. FDA should rank domestic and foreign facilities together, based on the risks that the products from each facility pose to the American consumer. If there are 100 foreign facilities with higher risk profiles than the highest-ranked domestic firm, the American consumer is ill-served unless those 100 foreign facilities are inspected before the domestic firm.

Foreign sites, particularly those owned by U.S. companies, would welcome more inspections of all foreign sites. This will only happen if FDA is required to have comparable inspection frequency for domestic and foreign facilities.

The U.S. market for pharmaceuticals is large and lucrative. FDA's recent action to restrict imported vegetable protein unless and until it could be shown to be free of melamine is evidence of its broad authority to prohibit the importation of products that appear to be adulterated. Furthermore, this is where FDA has an enforcement advantage with regard to foreign facilities versus domestic. It has no need to prove in an enforcement action that a product is adulterated. Imported products can be refused admission if they merely appear to be adulterated.

A second proposal is that FDA should consider a facility's foreign status per se as a risk factor in its risk-based inspection program. As I noted earlier and explain in greater detail in attachments to my written presentation, all statistics indicate that drugs sourced from foreign facilities pose greater risks to America's public safety. When a facility is inspected infrequently there is a natural tendency for management to become complacent. Maintaining cGMP compliance requires constant effort and vigilance, and it is a well-traveled road from minor deviations to serious quality failures.

Importantly, even if FDA conducts more frequent inspections of foreign facilities, we believe an additional risk factor should still be assigned for foreign facilities. As a practical matter, any inspection that provides prior notice, is constrained by travel arrangements, and suffers from the communications problems inherent when dealing with documentation that is in a foreign language while using a translator provided by the facility, is bound to be less effective than an unannounced inspection of indeterminate duration, conducted in the investigator's native tongue.

The Bulk Pharmaceutical Taskforce's third request is a stopgap measure that FDA could implement before it has the resources to conduct adequate foreign inspections. It could actively test and monitor the impurity profiles of active pharmaceutical ingredients produced in facilities that FDA has never inspected.

Allow me to elaborate here. New drugs require prior approval. Pre-approval inspections are part of that prior approval process, but not all drugs are new drugs. Drugs that are not new drugs do not require prior approval and do not require a pre-approval inspection. These are the facilities that are likely to never have any inspection, not a GMP inspection, not a pre-approval inspection. Further, there have been many prescription-to-over-the-counter switches in the past few years. One of the earliest of those switches was ibuprofen. In August 2002, FDA proposed to move ibuprofen from new-drug to not-new-drug status. In response to the Chairman's question about behind-the-counter drugs, and are we just moving more drugs into a non-approved status, the issue is really not whether it is Rx, OTC, or behind-the-counter, the issue is whether it is a new drug that at least has a prior approval inspection, or a not-new drug. And FDA's proposal would move more drugs into this uninspected, not-new-drug category.

To be sure, testing and monitoring would be a poor substitute for onsite inspections, but given budget and staffing considerations it would be a great improvement compared to doing nothing. Just as a stopped clock is correct twice a day, a non-GMP-compliant facility will periodically produce drugs that meet specifications. It is reasonable to assume that foreign manufacturers with sub-standard

cGMPs will cherry pick production lots and ship to the U.S. only ingredients that meet specifications. When different batches of products coming from the same facility have significantly different impurity profiles, it is reasonable to conclude that they did not come from a process that is in control.

Mr. STUPAK. Mr. Dubeck, I am going to have to ask you to wrap it up here, please.

Mr. DUBECK. Just that if FDA observes through monitoring of variable impurity profile, it could refuse admission on the basis that the products appear to be adulterated. We sympathize with FDA's resource limitations, but it is imperative that foreign manufacturing facilities be inspected at the same rate.

In closing, I note that although there are many economic factors that have resulted in nearly half of all drugs marketed in the U.S. being produced in foreign facilities, the fact that such production attracts less aggressive FDA oversight surely contributes to the trend. On behalf of SOCMA and the Bulk Pharmaceutical Taskforce, I thank you for your time and attention to this serious matter. I will be happy to answer questions.

[The prepared statement of Mr. Dubeck follows:]

UNITED STATES HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

Written Testimony of John B. Dubeck, Esq.,
Keller and Heckman LLP
on behalf of the
Bulk Pharmaceutical Task Force of the
Synthetic Organic Chemical Manufacturers Association
November 1, 2007

In January of last year, the Bulk Pharmaceuticals Task Force of the Synthetic Organic Chemical Manufacturers Association submitted a Citizen Petition to FDA urging that it take specific actions to better manage the manufacturing-related public health risks posed by the majority of pharmaceuticals consumed today. My testimony today will explain that these risks to the American consumer arise because inspections of foreign manufacturing facilities are so infrequent that the risk to a manufacturer of being found out of compliance is virtually non-existent. Given the magnitude of the problem, we are disappointed that the only communications we have received from FDA regarding the petition have been its administrative assignment of a docket number, *viz.*, 2006P-0049, and an equally administrative automatic notification approximately 180 days later stating that FDA had not yet reached a decision.[1]

By way of background, the Bulk Pharmaceuticals Task Force (also known as the BPTF) is an association for manufacturers of active pharmaceutical ingredients (also known as APIs), excipients, and intermediates. The BPTF is a subgroup within the Synthetic Organic Chemical Manufacturers Association – also known as SOCMA. SOCMA is the leading trade association of the specialty batch and custom manufacturing chemical industry, representing 300 member companies with more than 2000 manufacturing sites and over 100,000 employees.

[1] Pursuant to 21 C.F.R. §10.30(e)(2), FDA is required to respond to petitioners within 180 days, indicating either that the petition is approved, denied, or providing a tentative response indicating why FDA has been unable to reach a decision. FDA's response to the BPTF said that the Petition raised "significant issues requiring extensive review and analysis by Agency officials." See FDA's July 20, 2006 Response Letter at www.fda.gov/ohrms/dockets/dockets/06p0049/06p-0049-let0001-vol1.pdf.

Once the safety and effectiveness of a drug has been established, the only assurance that on-going production will yield products with the same assurance of safety and effectiveness is if the products are manufactured in accordance with current good manufacturing practice (cGMP).[2] Compliance with cGMP is the responsibility of the drug manufacturer. FDA determines whether a manufacturer is in compliance with its cGMP obligations by conducting inspections. A manufacturer's failure to adhere to cGMP renders a drug adulterated, *per se*, even if the drug product is analytically within specifications. This is an essential distinction between the quality assurance obligation imposed on drug manufacturers and mere quality control. The goal is to ensure that every single dosage is of appropriate quality, not just that specifications are met on average.

FDA is required to inspect domestic drug establishments every two years.[3] These inspections are unannounced. Indeed, BPTF members have had to abruptly alter plans to attend task force meetings because an FDA inspector had arrived at one of their facilities. A single inspection can extend over many weeks and may involve several separate visits of one or more days. The law imposes no comparable obligation on FDA to inspect foreign facilities. Since FDA must be invited to perform its official duties on foreign soil, a foreign facility always receives several weeks notice of an impending visit by an FDA investigator and the length of the inspection is typically driven by travel schedules rather than the compliance status of the facility. To FDA's credit, it is undisputed that its cGMP inspections are the most demanding in the world. Accordingly, the fact that the statute permits FDA to enter into cooperative arrangements with foreign officials to determine whether drug(s) should be refused admission into the United States[4] is a poor substitute for a visit by the FDA.

The drug manufacturing industry today is structured vastly different than it was thirty, twenty or even ten years ago. No longer are drugs primarily manufactured in-house by the major pharmaceutical companies and sold as branded products. The major pharmaceutical companies

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[2] *See* FDCA § 501(a)(2)(B).

[3] *See* FDCA § 510(h).

[4] *See* FDCA § 510(i).

have greatly expanded the number of manufacturing steps that are out-sourced (increasingly to foreign manufacturers). The ever expanding number of generic drugs available are even more likely to include significant components from (or be entirely produced by) a foreign source. By 2004, firms in China, Hong Kong and India accounted for 49% of the drugs consumed in the U.S. By 2005, four out of every ten prescriptions came from foreign facilities.[5] The percentage of active ingredients produced on foreign soil is substantially higher.

FDA's records indicate that in 2004 (the latest year for which reliable data is widely available), there were 3300 domestic drug manufacturing sites and 2700 foreign facilities.[6] China and India led in the number of facilities, with 440 and 300 sites, respectively.[7] In 2004, FDA conducted cGMP inspections on 1825 or 55% of the domestic facilities, but only 184 or just under 7% of the foreign facilities.[8]

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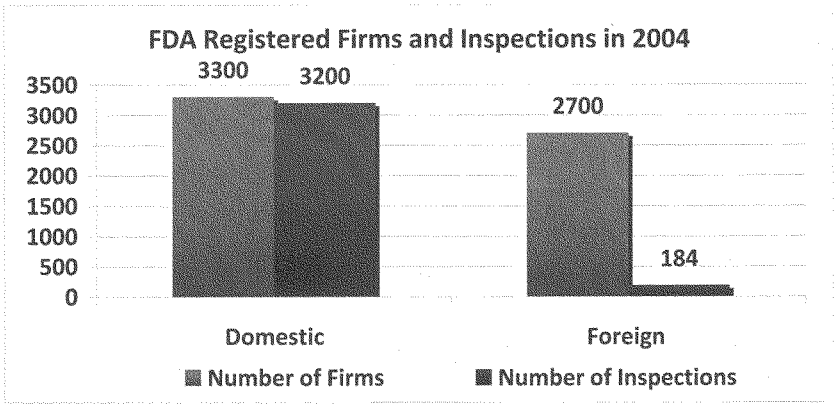
[5] *See* GOVERNMENT EXECUTIVE *at* http://www.govexec.com/dailyfed/1204/121404cdpm1.htm (*last visited* October 20, 2005). The proportion of APIs that are imported is even higher; at least 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported. *See* GAO/HEHS-98-21: General Accounting Office, GAO, Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives, Food And Drug Administration, *Improvements Needed in the Foreign Drug Inspection Program* (March 1998) [hereinafter 1998 GAO report].

[6] This number excludes the 4500 domestic sites registered solely for the production of medical gases.

[7] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[8] Source: CDER Reports to the Nation (for years 1999 to 2004).



As a practical matter, a foreign manufacturer is unlikely to be inspected for cGMP compliance at all except in the context of a pre-approval inspection. As I explain below, these pre-approval related cGMP inspections have less value than you might think with respect to assuring on-going compliance.

For purposes of understanding the various inspection statistics that have been reported by FDA and GAO, it is important to note that not all foreign drug establishments manufacture products that trigger a preapproval inspection. I will return to the significance of this later in the context of an FDA notice of proposed rulemaking related to over-the-counter dosage forms of ibuprofen.

Briefly, drugs that are not generally recognized as safe and effective and (even if so recognized) have not been used to a material extent and for a material time are defined to be New Drugs. New Drugs require prior approval of a New Drug (or Abbreviated New Drug) Application (NDA/ANDA) before they may be legally marketed. As a general rule, FDA inspects each site indentified in an NDA/ANDA that performs a critical production or quality control function prior to approving the application. Such pre-approval inspections look at the design and development of the manufacturing process and the adequacy of the systems in place to assure compliance with cGMP by that facility. It may or may not include an actual inspection of the management's ability to operate the facility in accordance with cGMP at production capacity. In

trying to best allocate scarce inspection resources, the responsible FDA field office may decide that the processes for manufacturing the product undergoing approval are so similar to an already inspected process at the facility that nothing of value would be gained by conducting an inspection; if a recent cGMP inspection of the site found no significant deficiencies for similar types of production operations, a new inspection for compliance with cGMP also may appropriately be skipped. The statistical discrepancy this creates between the number of New Drug Applications approved, the number of pre-approval inspections, and the number of cGMP inspections conducted by FDA is not a concern. More likely, however, is that the equipment and procedures in place to be inspected during a pre-approval inspection are only appropriate for or being operated at pilot scale.

There is a big difference between having procedures that may allow operations to comply with cGMP and actually implementing the procedures to achieve cGMP and maintaining operations at a high state of on-going compliance. Also, post-approval scale up changes may or may not require prior approval; even if prior approval of a supplemental NDA/ANDA is required, it does not follow that a new pre-approval inspection would be conducted; the cGMP status of a scaled up operation is typically only reviewed as part of a routine cGMP inspection. If a routine cGMP inspection is unlikely to occur in a timely fashion, it is very tempting for management to skimp on validating procedures and otherwise paying close attention to cGMP requirements. If the first routine cGMP inspection does not occur for another 12 years, the degree of control exercised during the scale up process and early production will be ancient history.

Statistics presented at a cGMP Conference in 2005 indicate that cGMP inspections of foreign firms result in significantly more violations than seen in domestic firms.[9] When comparing pre-approval inspections, the same discrepancy is seen: deviations from cGMP were more serious in foreign facilities than in U.S. facilities.[10] These numbers cry out for FDA to conduct more frequent inspections of foreign facilities and underscore the significance of the factors indentified

[9] *See id.*; *see also* Philip S. Campbell, *2004 Inspection Records & Compliance Issues*, 29th International cGMP Conference, Univ. of Georgia, March 2005.

[10] *See* 1998 GAO report, *supra* note 5.

in the BPTF petition which uniquely invite managers of foreign facilities to spend less time, attention and money on ensuring that manufacturing operations comply with cGMP. A drastic and dramatic overhaul of FDA's approach to the risks posed by foreign manufactured drugs is long overdue. The manufacturing side of the pharmaceutical industry has changed substantially in recent years and yet FDA's allocation of inspection resources remains unchanged from an earlier era.

In order for FDA to give cGMP inspections of foreign facilities the priority it deserves, the BPTF proposes that FDA do three things. Our first proposal is that FDA should abandon its policy of separately prioritizing facilities for inspection based on whether they are domestic or foreign facilities.[11, 12] Instead, FDA should rank domestic and foreign facilities together, based on the risk that products from each facility pose to the American consumer. If there are 100 foreign facilities with higher risk profiles than the highest risk-ranked domestic firm, the American consumer is ill-served unless those 100 foreign facilities are inspected before the domestic firm. This obviously would require either an easing of the demand that domestic facilities be inspected every two years, which would allow a reallocation of scarce resources, or it would necessitate additional funding.

Some may argue that unified rankings will be problematic because fair implementation would require equal access to foreign and domestic facilities, something that is not within even Congress' authority to grant. The U.S. market for pharmaceuticals is large and lucrative. As recently evidenced by the import restrictions FDA implemented with respect to melamine contaminated proteins, FDA already has broad authority to refuse the importation of any product that appears to FDA to be adulterated. It is arguably within FDA's discretion to determine that a refusal to allow an inspection of a foreign facility creates the appearance of non-compliance, and that therefore it is permissible to refuse imports from the facility until an inspection is allowed. While such a policy would likely have trade implications and could subject U.S. manufacturers

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[11] *See* presentation by Alicia Mozzachio, FDA inspector, *APIs and the Foreign Inspection Program*, at SOCMA's cGMP Compliance Conference for Pharmaceutical Ingredient Suppliers, Oct., 6, 2005; *see also* Pat Phibbs, *U.S., Foreign Firms Ranked Separately in Tool FDA Uses to Target Inspections*, Daily Report for Executives, Oct. 11, 2005.

[12] *See* FDA's *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model* (September, 2004), *available at* http://www.fda.gov/cder/gmp/gmp2004/risk_based.pdf.

to retaliatory prohibitions on their efforts to export to other countries, the health justification for the policy and the ease with which such refusals could be avoided make it seem reasonable that diplomatic solutions to these concerns could be reached.

Our second proposal is that FDA should specifically list "foreign facility" as a significant risk factor in its risk-based inspection program. As noted in the BPTF petition and as borne out by the statistics noted above, foreign facilities, in general, pose a greater risk to public safety. When a facility is inspected infrequently, there is a natural tendency for management to become complacent. In the absence of a credible threat of reasonably frequent inspections, the "c" in cGMP gets lost. Maintaining cGMP compliance requires constant effort and vigilance. Minor deviations may not cause any apparent lack of quality, but it is a well-traveled road from minor deviations to serious quality failures. Since each step away from cGMP compliance can be a short term cost savings, profits can displace cGMPs in the absence of creditable regulatory oversight.

If the frequency of foreign inspections were increased proportionate with risk, an additional (but smaller risk factor) should still be assigned to foreign facilities. As a practical matter, any inspection that provides prior notice, is constrained by travel arrangements and therefore must be concluded within a defined window of time, and suffers from the communications problems inherent when dealing with facilities that operate in a foreign language through a translator provided by the facility, is bound to be less effective than an unannounced inspection of indeterminate duration conducted in the investigator's native language.

The final request in the citizen petition is that FDA actively monitor the impurity profiles of active pharmaceutical ingredients (APIs) produced in facilities which FDA has not inspected. This monitoring would be a poor substitute for on-site inspections, but given budget and staffing considerations, it would be a great improvement compared to doing nothing to assure the safety of these important drug components. As noted above, cGMP is all about assuring quality; it is much more demanding than simply determining that the final product meets specification when sampled at some defined frequency and sample size. Just as a stopped clock is correct twice a day, a process that is not in compliance with cGMP will produce product that meets specifications occasionally. It is reasonable to assume that non-cGMP-compliant foreign

manufacturers will cherry-pick production lots and ship to the U.S. only those lots that meet specifications. Impurity profiles are highly sensitive to minor process variations. An active ingredient manufactured in accordance with cGMP will have a consistent impurity profile, while cherry-picked production from a non-complaint process will vary widely. It is virtually impossible to deconstruct an impurity profile to reconstruct the process conditions that created it, but one does not need that degree of knowledge to know that two different batches of product coming from the same facility with significantly different impurity profiles did not come from a process that is in control. If FDA gathered samples and discovered that products from a particular facility had variable impurity profiles, it would be justified in concluding that the facility was not being operated in accordance with cGMP. Therefore, the product would "appear" to be adulterated and future imports could be summarily refused admission until an inspection visit could be arranged and the presumption of non-compliance rebutted.

This monitoring of imports for a consistent impurity profile is an interim solution at best. It would raise production costs and reduce that amount of material available for export from a foreign manufacturer since even fewer batches could be cherry-picked if a consistent impurity profile is an additional requirement. Also, such monitoring is only useful for bulk active ingredients. Once an active ingredient is formulated with other ingredients, the impurity profile will reveal little about the control involved in the manufacturing process because of the presence of additional ingredients; their associated impurities will overwhelm the relatively subtle variations that can serve as a window on the degree of control inherent in the manufacturing process.

As noted above, not all drugs are subject to the new drug approval process and its associated prior approval inspection. Many of these "non new" drugs as available over-the-counter and are lawfully marketed as long as their composition and labeling are consistent with a final or tentative final monograph or an applicable enforcement policy pending adoption of a final monograph.[13] Because there are no regulatory pre-approval barriers to entry for these products, formulators are free to obtain raw materials from any manufacturer and may change suppliers

[13] 21 C.F.R. Part 330.

freely and frequently to obtain the lower costs. Quality assurance is a good investment only if there is a higher price to pay for poor quality. In the absence of effective oversight, quality assurance investments become unnecessary and unrecoverable costs. As long as the only production of imported mongraphed products (or ingredients) that are offered for import to the U.S meet the applicable specification requirements of the U.S. Pharmacopeia, there is virtually no incentive for such manufacturers even to implement cGMP, let alone invest the time and attention required to stay up to date with cGMP.[14]

Indeed, if an OTC product or its components are manufactured in a foreign facility, the risks to public health are further amplified. The use of unproven or hazardous excipients in the formulations is possible because there currently is no systematic mechanism for detection or prevention of their use in such products. Additionally, just because adverse events are not associated with a particular drug product does not mean such product does not pose additional risks. Adverse events are difficult to correlate to an actual source or problem, especially considering that many OTC manufacturers may use numerous different suppliers over time for the same product with the same API and adverse effects of poor quality OTCs could take considerable time to appear.

We sympathize with FDA's limitations in resources, but believe that if the agency is to fulfill its mandate to protect US consumers, it is imperative that the foreign manufacturing facilities responsible for exporting 80% of the bulk APIs into U.S. be inspected, at a minimum, to the same extent as domestic facilities. As Bernard Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner of FDA in 2001 stated, "FDA must improve foreign inspection and physical inspection coverage and oversight of foreign producers to be able to maintain the safety of products on that [sic] market that we believe Americans expect and demand."[15]

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[14] Although it is common for drug product manufacturers in the U.S. to qualify their suppliers, there is no explicit regulatory requirement for such inspections. *Cf.*, 21 C.F.R. Part 211.

[15] Bernard Schwetz, D.V.M., Ph.D, Acting Principal Deputy Commissioner, FDA, Testimony before the U.S. House of Representatives Committee on Appropriations, Subcommittee on Agriculture, Rural Development, and Related Agencies, March 8, 2001.

Although there are many economic factors that have resulted in nearly half of all drugs marketed in the U.S. being produced in foreign facilities, the fact that such production attracts less aggressive FDA oversight surely contributes to the trend. A significant and prompt reordering of priorities by FDA with respect to the inspection of foreign facilities is essential to protect Americans from facing more crises due to unsafe drugs. Absent a new approach to inspecting imported products, the risks to public health will only increase.

In closing, I would like to note that the number of drugs entering the country without any oversight of their manufacturing process is likely to increase further and even more creative enforcement techniques than outlined in the Citizen Petition may be necessary. A factor that is expected to drive this increase is the fact that a number of prescription drugs have been converted to OTC status. One of the earliest such switches was the OTC dosage for ibuprofen. In August 2002, FDA proposed to substantially deregulate the manufacture of the 200 mg tablet form of ibuprofen by adding it to the monograph for internal analgesics. If this rule making were to be finalized as proposed, bulk ibuprofen would freely enter this country without FDA having any clue as to the manufacturing process employed or the degree of manufacturing control that existed. The impurity profiling technique described above is unlikely to be effective since it will be just as easy (and more profitable for the foreign manufacturer) to import fully formulated dosage form product. In short, FDA is proposing to allow ibuprofen of unknown quality to be sold in the U.S. without any prior approval on the basis that such products are generally recognized as safe and effective and have been used to a material extent and for a material time.

This ibuprofen proposal is significant for two reasons. First, it is a landmark event; there are many drugs that have made the Rx to OTC switch since ibuprofen and, in time, will also have been on the market for a material time and extent. They will all be candidates for conversion to "not new" drug status. Second, the same blind spot that allows FDA to ignore the risks of improperly manufactured imported drugs underlies the FDA proposal. The products that have created a favorable record of safety and effectiveness over a material time and extent have all been manufactured under the strict controls of the NDA/ANDA process. Further, the ibuprofen API used in these products for this material time and extent has been produced to an

overwhelming extent in a limited number of domestic establishments and FDA has a history of demanding more detailed information from these manufacturers than simple compliance with the specifications in the United States Pharmacopaeia (USP). How this history supports the notion that uncontrolled manufacture of product that may only nominally meet USP specifications constitutes uses for a material time and extent of a generally recognized as safe product is a mystery. Although the context is different, it is the same mystery that concerns the Subcommittee today and suggests that the issue runs deeper than simply a lack of funding to perform more frequent inspections of foreign facilities.

On behalf of SOCMA and its Bulk Pharmaceuticals Task Force, I thank you for your time and attention to this serious matter.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Petition to Request the Food and Drug Administration to Rank Foreign and Domestic Drug Manufacturing Firms Together for Purposes of the Agency's Risk-Based Approach to Inspections and Take Other Steps to Reduce the Public Health Risks Associated with Imported Drugs	)	Docket No. _____

CITIZEN PETITION

The Synthetic Organic Chemical Manufacturers Association's (SOCMA's) Bulk Pharmaceuticals Task Force (BPTF) submits this petition to request that the Food and Drug Administration (FDA) take specific actions designed to allow it to better manage the risks to public health associated with the use of drugs manufactured or processed at foreign facilities.

The BPTF is an association for manufacturers of active pharmaceutical ingredients (APIs), excipients, and intermediates. The BPTF's primary objective is to seek clarification of current regulatory requirements and to interact with governmental agencies on emerging issues that may impact SOCMA members. SOCMA is the leading trade association of the specialty batch and custom manufacturing chemical industry, representing 300 member companies with more than 2000 manufacturing sites and over 100,000 employees.

I. ACTION REQUESTED

The BPTF respectfully submits this petition to request the Commissioner of Food and Drugs to allocate its resources to reduce the public health risk that imported drug products pose by:

1. ranking foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections;
2. listing "foreign facility" as a significant risk factor for purposes of its risk-based approach; and
3. implementing a program of monitoring the impurity profiles of imported over-the-counter (OTC) drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP), so that FDA may refuse entry under 21 U.S.C. § 381(a) to products that appear adulterated.

2006P-0049 CP1

II. STATEMENT OF GROUNDS

A. Background

Domestic and foreign establishments importing drugs must register their establishment and list all drugs in commercial distribution.[1] A review of establishment registrations and drug lists reveal several important trends in drug manufacturing. In 2004, 2700 foreign drug manufacturing establishments were registered with the FDA versus 3300 domestic sites (excluding the 4500 domestic sites registered solely for the production of medical gases).[2] China and India led in the number of FDA registered facilities with 440 and 300 sites, respectively.[3] Approximately 51% of the registered foreign sites are API manufacturing facilities; the remaining are other establishment types, such as finished dosage plants and control laboratories.[4]

The number of finished drug products manufactured abroad for the U.S. market is increasing, accounting for four of ten prescriptions drugs now sold in this country.[5] A review of the FDA Type II DMF database also reflects the trend toward increasing foreign drug manufacturing: 87 percent of the 510 DMFs filed with the FDA in fiscal year 2004 were for products/APIs manufactured outside of United States.[6] Even if not all of these DMFs have yet been cross-referenced into approved applications, the numbers suggest that a greater proportion of drugs are likely to come from foreign countries in the future.

FDA is responsible for ensuring that all domestic and imported drug products are safe, effective, and in compliance with current good manufacturing practices (cGMPs).[7] It is cGMP that provides the assurance that each pill we consume has the same identity and strength and the same quality and purity characteristics as the product approved by FDA. FDA is required to inspect registered domestic establishments in any state every two years.[8] NDA/ANDA pre-approval inspections are conducted for specific new products, but domestic facilities also receive periodic, unannounced inspections for cGMP compliance. Based on CDER inspection statistics of 1999-2003 (Table I below), and the estimated number of domestic manufacturing sites registered, it

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[1] *See* Federal Food, Drug and Cosmetic Act (FDCA) § 510, 21 C.F.R. § 207.20, 21 C.F.R. § 207.20.

[2] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005.

[3] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[4] *See id.*

[5] *See* GOVERNMENT EXECUTIVE *at* http://www.govexec.com/dailyfed/1204/121404cdpm1.htm (*last visited* October 20, 2005). The proportion of APIs that are imported is even higher; at least 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported. *See* GAO/HEHS-98-21: General Accounting Office, GAO, Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives, Food And Drug Administration, *Improvements Needed in the Foreign Drug Inspection Program* (March 1998) [hereinafter 1998 GAO report].

[6] www.fda.gov/cder/dmf/index.htm

[7] *See* FDCA § 501(a)(2)(B).

[8] *See* FDCA § 510 (h).

appears that FDA is reasonably close in meeting the biennial inspections mandated of the domestic facilities.

Table I
CDER Manufacturing Plant Inspections

Fiscal Year	Domestic Inspections		Foreign Inspections
	NDA/ANDA	cGMP	
1999	2548	1844	220
2000	2229	1436	248
2001	2090	1497	249
2002	2166	1519	210
2003	1453	1512	184
2004	1375	1825	184

Source: CDER Reports to the Nation (for years 1999 to 2004)

FDA is not required to inspect foreign facilities every two years for the simple reason that FDA has no authority to enter a facility in a sovereign country unless invited. As partial compensation for FDA's lack of authority to inspect foreign facilities, the statute invites FDA to enter into cooperative arrangements with foreign officials to determine whether drug(s) should be refused admission into the United States.[9] Nonetheless, FDA is falling short of meeting its responsibility to safeguard the public from adulterated or misbranded drugs manufactured or processed at foreign facilities. Even though as much as 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported,[10] the Agency inspects foreign API suppliers and foreign suppliers of drug products for OTC applications infrequently, if at all. Indeed, inspections of foreign pharmaceutical manufacturers occur with far less frequency than the two-year interval Congress deems necessary for domestic manufacturers.

In fact, at the current rate of inspection, a foreign manufacturer is unlikely to be inspected for cGMP compliance at all, unless the firm is listed in an ANDA/NDA. In October 2000, Jane M Henney, M.D. testified before the Subcommittee on Oversight and Investigation that based on the Establishment Evaluation System database, 242 foreign API manufacturers, in 36 countries, appeared to have exported products into the U.S. in 1999, without having been inspected by FDA.[11] Forty-six of these firms were located in China and Hong Kong and eleven in India; according to 2004 data, firms in these countries now account for 49% of the drugs consumed in the U.S. It is worthy to note that the final rule requiring registration of foreign establishments did not take effect until February 11, 2002; therefore, the actual number of foreign facilities not inspected by the FDA may have been substantially higher than 242.

According to FDA's Center for Drug Evaluation and Research (CDER) Office of Compliance, 90 percent of the international drug inspections of facilities were limited to "pre-approval"

[9] *See* FDCA § 510 (i).

[10] *See* 1998 GAO report, *supra* note 5.

[11] Jane M. Henney, M.D., Testimony to Chairman Fred Upton, Subcommittee on Oversight and Investigations, House of Representatives, October 3, 2000.

inspections, with the remainder being cGMP compliance or post-approval surveillance.[12] Thus, a majority of the foreign drug manufacturing sites were not inspected for cGMP compliance at all, and those that were inspected had little or no follow-up on the corrective action implemented in response to previous inspections.

In China and India, for example, more than five years may elapse between FDA inspections of a drug manufacturer. Moreover, FDA is still experiencing delays in taking enforcement action against foreign pharmaceutical manufacturers. In one case, FDA allowed a manufacturer in India to continue exporting its products to the United States despite an investigator's finding that the manufacturer could not adequately test for impurities in its product and water system; nearly two years passed before FDA determined that enforcement action had never been taken against this manufacturer.[13]

Statistics also show the number of Form 483s issued to foreign firms after an inspection is significantly higher in percentage than are issued to domestic firms[14] and serious deviations from GMPs were identified more often in foreign than U.S. pre-approval inspections.[15] If there had been enough cGMP inspections of foreign firms to generate comparable statistics, it is reasonable to assume that the higher violation rate for foreign facilities would be repeated.

Foreign facilities, in general, pose a greater risk to public safety because when a facility is inspected infrequently, as is the case for foreign manufacturers, there is a natural tendency for management to become complacent that what was adequate at the last inspection is still adequate. In the absence of a credible threat of reasonably frequent inspections, the "c" in cGMP gets lost. Maintaining cGMP compliance requires constant effort and vigilance. Minor deviations may not cause any apparent lack of quality, but it is a well-paved road from minor deviations to serious quality failures. Each step away from cGMP compliance appears to be a short term cost savings. Without creditable regulatory oversight, profits can displace the assurance of cGMP. Furthermore, the consequences for a foreign firm that fails an FDA inspection is loss of the US market; however, if a foreign firm complies with local laws, it may continue to operate and produce for its own domestic, and many other, markets. This, of course, is not the situation for U.S. drug manufacturers, which risk a much greater penalty for failing FDA inspections.

B. Risk-Based Inspection Ranking

FDA has stated that as part of its cGMPs for the 21st Century Initiative, it will pilot a risk-based inspection model for prioritizing drug manufacturing establishments for routine inspection.[16] We

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[12] Charles M. Edwards, *FDA International Inspections*, 27th International cGMP Conference, Univ. of Georgia, March 2003.

[13] *See* 1998 GAO report, *supra* note 5.

[14] *See id.*; *see also* Philip S. Campbell, *2004 Inspection Records & Compliance Issues*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[15] *See* 1998 GAO report, *supra* note 5.

[16] *See* FDA's *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model* (September, 2004), *available at* http://www.fda.gov/cder/gmp/gmp2004/risk_based.pdf.

understand that as part of this initiative, the Agency has started using a computer program to select manufacturers for inspection, which ranks domestic facilities, using risk factors such as specific product, processes used, recalls, violation history, and contamination potential.[17] We also understand that the agency will use this program for foreign manufacturers in 2006, but will rank domestic and foreign facilities separately.[18] In this regard, we urge FDA to risk-rank domestic and foreign facilities together. Additionally, we request that, based on the considerations noted above, the Agency specifically list "foreign facility" as a significant risk factor for purposes of its risk-based approach to inspections. Such action will assure that resources are actually allocated consistent with the risk, and thereby reduce the likelihood that quality problems associated with drugs would lead to injury, and even death, as happened in 1998-1999, when seventeen patients who were treated with gentamicin sulfate died – the common denominator linked to the deaths was the API of the drug originated from a Chinese supplier with varying levels of endotoxin and notable chemical impurities.[19]

One difficulty that may be perceived with risk ranking foreign and domestic firms together, however, is FDA's lack of authority to demand access to foreign facilities. In theory, this lack of authority could undermine the unified rankings because FDA would have to skip over facilities to which it could not gain access. In our opinion, this problem is more theoretical than real, at least in the case of facilities that are named in approved New Drug Applications. Foreign facilities that supply NDA holders typically establish Drug Master Files (DMFs) that describe the portions of the chemistry, manufacturing, and control operations associated with new drug production performed at the site. Because information provided in a DMF is incorporated by reference into the customer's New Drug Application, if a supplier were to deny access to FDA, for example to check records, the customer's NDA would be in jeopardy. As a result, the relationship between supplier and NDA holder (customer) gives FDA leverage over the suppliers—leverage that can be used to gain access to foreign suppliers.

C. Impurity Monitoring as a Surrogate for cGMP Inspections

A different approach, however, is required for foreign establishments that supply products other than those subject to a NDA. Most over-the-counter (OTC) drugs are not the subject of NDAs and ANDAs; rather, they are marketed pursuant to regulations referred to as "monographs" or an enforcement policy pending adoption of a final monograph.[20] Because there are no regulatory pre-approval barriers to entry for these products, formulators are free to source raw materials from any manufacturer and may change suppliers freely and frequently to obtain the lowest cost of goods. Quality assurance is a good investment only if there is a higher price to pay for poor

[17] *See* presentation by Alicia Mozzachio, FDA inspector, *APIs and the Foreign Inspection Program*, at SOCMA's cGMP Compliance Conference for Pharmaceutical Ingredient Suppliers, Oct., 6, 2005; *see also* Pat Phibbs, *U.S., Foreign Firms Ranked Separately in Tool FDA Uses to Target Inspections*, Daily Report for Executives, Oct. 11, 2005.

[18] *See id.*

[19] A review of all the evidence indicated it was unlikely that endotoxin alone was responsible, but that it might have acted synergistically with a non-endotoxin pyrogen. *See* James F. Cooper, LAL TIMES, *Pyrogenic Reactions to IV Gentamicin*, December 1999; *see also* Steve Sternberg, USA TODAY, *FDA Probe Into Antibiotic Deaths Called Inadequate*, May 11, 2000.

[20] 21 C.F.R. Part 330.

quality. In the absence of effective oversight, quality assurance investments become unnecessary and unrecoverable costs. As long as the only production of imported mongraphed products (or ingredients) that are offered for import to the U.S meet the applicable specification requirements of the U.S. Pharmacopeia, there is virtually no incentive for such manufacturers to even implement GMP, let alone invest the time and attention required to stay up to date with cGMP.[21]

Indeed, if an OTC product or its components are manufactured in a foreign facility, the risk factors discussed above with respect to foreign suppliers to NDA/ANDA holders are further amplified. At this time, use of unproven or hazardous excipients in the formulations is possible because there currently is no systematic mechanism for detection or prevention of their use in such products. Additionally, just because adverse events are not associated with an OTC, does not mean there are no additional risks associated with foreign sites. Adverse events are difficult to correlate to an actual source or problem, especially considering that many OTC manufacturers may use numerous different suppliers over time for the same product with the same API and adverse effects of poor quality OTCs could take considerable time to appear.

Since cGMP non-compliance can be inferred by observing inconsistent impurity profiles in different batches of products, we ask that FDA implement a program to monitor the impurity profiles of imported OTC drugs for patterns that create the appearance of underlying cGMP violations. We recommend that FDA coordinate the priorities for this program based on the risk ranking of the facility that produces the product.

D. Conclusion

While the FY 2006 budget was signed into law on November 10, 2005,[22] we understand that the 2006 budget with regard to the foreign inspection programs is still unclear but, based on the proposed 2006 budget,[23] likely includes cuts to nearly all FDA's inspection programs, potentially reducing the foreign drug establishment inspection program by 5.8%. We sympathize with FDA's limitations in resources, but believe that if the agency is to fulfill its mandate to protect US consumers, it is imperative that the foreign manufacturing facilities responsible for exporting 80% of the bulk APIs into U.S. be inspected, at a minimum, to the same extent as domestic facilities. As Bernard Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner of FDA in 2001 stated, "FDA must improve foreign inspection and physical inspection coverage and oversight of foreign producers to be able to maintain the safety of products on that [sic] market that we believe Americans expect and demand."[24]

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[21] Although it is common for drug product manufacturers in the U.S. to qualify their suppliers, there is no explicit regulatory requirement for such inspections. *Cf.*, 21 C.F.R. Part 211.

[22] *See:* PL 109-97 http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=109_cong_public_laws&docid=f:publ097.109.pdf

[23] Julie Appleby, USA TODAY, *Budget Cuts FDA Safety Checks*, Feb.14, 2005.

[24] Bernard Schwetz, D.V.M., Ph.D, Acting Principal Deputy Commissioner, FDA, Testimony before the U.S. House of Representatives Committee on Appropriations, Subcommittee on Agriculture, Rural Development, and Related Agencies, March 8, 2001.

We urge FDA to properly allocate its limited resources to reduce the overall risk to consumers. FDA could increase the compliance stakes for foreign establishments by more aggressively exercising its prerogative under 21 U.S.C. § 381(a) to refuse entry to products that appear adulterated. Warning Letters and resource consuming formal enforcement efforts are not prerequisites to keeping suspect foreign drug products out of domestic commerce. Exercising this prerogative does not impose a significant burden on the budget and will raise the compliance stakes for foreign manufactures.

Although nearly half of all drugs marketed in the U.S. are produced or manufactured in foreign facilities, and this number is rapidly increasing, the vast majority of FDA inspections occur domestically. Neglecting to adequately inspect foreign drug establishments not only places domestic pharmaceutical manufacturers at an economic disadvantage, it also clearly places U.S. consumers and patients at risk. Contaminated gentamicin from a foreign drug supplier was the apparent cause of seventeen deaths in 1998-1999. Arguably, insufficiently aggressive foreign drug establishment inspections led to the flu vaccine shortage last fall. In order to help protect Americans from facing more crises due to unsafe drugs, the BPTF urges FDA: 1) to utilize its authority to refuse entry under 21 U.S.C. § 381(a) to products that appear adulterated; 2) to rank foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections; 3) to list "foreign facility" as a significant risk factor for purposes of its risk-based approach; and 4) to implement a program of monitoring the impurity profiles of imported over-the-counter (OTC) drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP).

III. ENVIRONMENTAL IMPACT STATEMENT

The action requested does not involve the introduction of any substance into the environment and is subject to categorical exclusion of 21 C.F.R. § 25.30(a) because it involves inspections. To the petitioner's knowledge, no extraordinary circumstances exist.

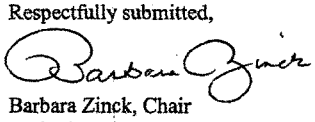
IV. ECONOMIC IMPACT STATEMENT

An economic impact statement is not required at this time.

* * *

The undersigned certify that, to the best of her knowledge and beliefs, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,



Barbara Zinck, Chair
Bulk Pharmaceuticals Task Force

Mr. STUPAK. Thank you, Mr. Dubeck. Mr. Downey, please, for opening statement. Your full statement is in the record, so if you could summarize and keep it to five minutes, we would appreciate it.

TESTIMONY OF BRUCE DOWNEY, CHAIRMAN AND CEO, BARR PHARMACEUTICALS, INC., AND CHAIRMAN, GENERIC PHARMACEUTICAL ASSOCIATION

Mr. DOWNEY. Yes, thank you, Mr. Chairman. I am Bruce Downey. I am Chairman and CEO of Barr Pharmaceuticals. Barr produces hundreds of prescription drugs here in the United States and Europe, both brand and generic, both finished goods and APIs, so I think we have a broad range of experience that is relevant to the committee's consideration today. In fact, in the U.S., we market nearly 5 to 6 billion tablets a year, so we have quite a bit of experience. I am also chairman of the GPhA, which is a generic trade association which represents companies that produce over 95 percent of the generic pharmaceuticals sold in the United States.

And I would like to comment on one part of the testimony earlier this morning. I think it is not correct to say that you can't buy products that aren't made in China. I mean, if you look at the largest members of our association, Barr, Watson, Teva, Mylan, Sandoz, none of those companies make finished goods in China, and the overwhelming majority are made either in the United States or Europe or Israel. So I think that part of the testimony wasn't correct.

But it is important to testify today on the committee's issue of FDA foreign inspections, and I think one thing is clear to me, and I think it was clear to the panels before me, that there is no justification for having fewer inspections of foreign facilities than we have of domestic facilities. And I say that as someone who is responsible for both. They pose equal risks. There just simply is no justification for that.

The question I think is most important is what is the appropriate level of oversight, and what are the different kinds of risks we are trying to manage? And I think there was some confusion this morning in testimony about two very different kinds of risks that require two very different kinds of responses. One risk is, in terms of number of incidents, is quite small. That is the risk of counterfeit. Compared to lawfully produced drugs, it is a quite small amount, but it is also the group that proposes the greatest risk. And inspection is not the answer to counterfeit drugs. People who make counterfeit products don't register their facilities in the database at FDA, the 6,000 or 3,000-firm database. They try to avoid detection, so the response for counterfeiting is to discover the counterfeiter and put them out of business. I mean, inspection is really not the issue. And the second issue is how do you review the compliance of lawful manufacturers, who have registered with the FDA, who have gone through the FDA approval process, and what is the appropriate role of inspection in monitoring their compliance with their overall commitments?

I think that, first and foremost, we have to allocate the amount of resources necessary to ferret out and put counterfeiters out of business. They pose the greatest risk, and that isn't necessarily for-

eign inspectors so much as investigators, the criminal investigation group at FDA, international law enforcement authorities, and I think there we need to provide whatever resources are necessary to make sure that risk is completely covered.

If you look at the second risk, the risk posed by FDA-regulated companies, I think today Mr. Hubbard mentioned, and I think he is right, we have an incredibly safe system. We have a system because testing and inspection is only one very small component of the overall FDA-regulated process. Now I would just like to go through it for you so you get a sense of how comprehensive it is.

In the development area, for example, we inspect all of our raw material suppliers' active ingredients before we even take in samples. Once we receive the samples, we work with the raw material manufacturers developing appropriate specifications for that compound, which are incorporated into our section of either the NDA or the ANDA file at FDA, and our raw material supplier incorporates that in the DMF, which is filed with the FDA. Those specifications and all the other components of the application are reviewed and approved by the FDA, and our commitment is to manufacture our products in conformity with those specifications and the processes that are part of our application.

Once the application is approved, and we continue to market the product, we routinely inspect our raw material suppliers, on average about every 3 years. We have a staff of 12 inspectors, covering the globe, inspecting our raw material suppliers, and they are supported by support staff and the like. So we do that self-policing, and FDA expects us to do that self-policing. I think it is different in the toy industry or other kinds of industries. That is the requirement of part of our obligation to be in FDA compliance, and we take that very seriously.

And once we are in production, as we receive lots of raw material, we receive a certificate of analysis from our producer, and we retest that lot so that we confirm the test results obtained by the raw material supplier, and then as that raw material is incorporated into finished goods, it is tested in process, and it is tested as finished good release and ultimately tested on stability to ensure that it remains potent through its shelf life. So there is an enormous amount of testing in the Rx system that ensures that products that we sell and present to consumers meet the requirements that we have in our applications.

And then once we get into post-marketing, we have to monitor adverse events, we have to investigate complaints we receive from pharmacists, physicians, patients. We conduct annual reviews on all of our products which analyze the test results of all the batches from the previous year, compare them with batches from years before that. We look at any complaints we have received and the adverse events. So we have a comprehensive review on each, individual product to satisfy ourselves that the product is being made safely and appropriately.

So I think in terms of inspections in the United States, we have five production facilities, and we have had seven inspections, GMP inspections, in the last 18 months. If you look abroad, I think you heard the testimony today, it is far less frequent, and I think the key element that I would like to leave you with is there is just sim-

ply no justification for that. I think that we have a very safe system because of all the safeguards built in. Inspections are one component, but not even the most important component of that system. It is important, but it should be spread evenly across the globe.

I would say that, if I were in charge of the overall inspection program and I heard the testimony today, I would tomorrow morning reallocate resources that were being used to inspect domestically to foreign inspections, because there is no justification for that disparity, and I would then try and work to get the additional resources to have all the facilities inspected at the frequency that we thought would be appropriate. And I think there are different ways to raise those resources. One is the direct appropriations. Second is through a user fee program that could be expanded to generic products and to raw material suppliers. And then third is your legislation, Mr. Stupak. I would think that is a way to raise the funds. I don't think it is probably the preferred way, and I would suggest that the focus not be on further testing of the material but in developing the infrastructure that was described this morning, the computer systems to monitor products as they move through the system, and ultimately to have enough inspectors to conduct the frequency of inspections you would like to have both here and abroad.

Just one last point, I think there is no justification either for having a different standard for OTC products and Rx products. We are generally in the Rx business, but people take products either way, and I think they pose similar risks and should be similarly treated.

[The prepared statement of Mr. Downey follows:]

TESTIMONY OF

BRUCE L. DOWNEY

CHAIRMAN AND CEO, BARR PHARMACEUTICALS, INC.

"FDA FOREIGN DRUG INSPECTION PROGRAM: A SYSTEM AT RISK"

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES
NOVEMBER 1, 2007

Good morning Chairman Stupak, Ranking Member Whitfield and Members of the House Subcommittee on Oversight and Investigations. Thank you for inviting me to discuss FDA's Foreign Drug Inspection Program – a program that is critical to ensuring the integrity of the American drug supply.

My name is Bruce Downey and I am Chairman and Chief Executive Officer of Barr Pharmaceuticals, a leading global manufacturer of generic and brand name prescription drugs, as well as over-the-counter medicines. Barr currently operates in more than 30 countries, with manufacturing and packaging operations of finished dosage forms in multiple sites in the United States, and manufacturing of Active Pharmaceutical Ingredients (APIs) and finished dosage form products in Croatia, Poland and the Czech Republic.

I am also Chairman of the Generic Pharmaceutical Association, which represents domestic and multinational companies that manufacture ninety (90) percent of the FDA-approved generic pharmaceuticals dispensed in the United States, as well as active ingredient suppliers for this market.

The U.S. generic pharmaceutical industry is committed to ensuring that the medicines we provide to consumers are of the highest quality and safe and effective for their intended use. In the United States, patients have rightfully come to expect that when they go to their local pharmacy counter they will receive the highest quality, FDA-approved prescription drug products in the world.

Millions of Americans rely on FDA-approved medicines everyday to improve their quality of life, treat illnesses and extend life. High-quality, affordable FDA- approved generic drugs have opened the doors for access to needed medicines for countless of our citizens, especially seniors, many of whom could not previously afford their medications. The record is clear that FDA-approved generic drugs consistently offer the same quality, safety and therapeutic effectiveness as their brand counterparts and, in the process, save tens of billions of dollars each year for insurers, taxpayers, Medicaid and Medicare, and cash-paying consumers.

I believe that I can speak on behalf of the generic pharmaceutical industry when I assure this committee that our industry invests hundreds of millions of dollars annually into state-of-the-art research and development and manufacturing facilities; maintaining complex operational infrastructures to ensure product

quality and efficacy; retaining highly skilled and dedicated employees; and developing and implementing extensive quality control systems. Last year, 63% of the 3.6 billion new and renewal prescriptions dispensed in the U.S. were filled with generics. That's approximately 2.3 billion generic prescriptions that were used safely and effectively by patients and consumers across the country.

We manufacture our products to exacting standards -- lot-to-lot -- that have been reviewed and approved by FDA through the drug application process. Over the last decade, our highly regulated industry has demonstrated its commitment to adhering to the highest quality standards for prescription drugs in the world – and our compliance track record over the last five years is second to none.

As Chairman of a multinational, global company, I'm here today to applaud the bipartisan efforts of this Committee in taking an affirmative oversight role with respect to the integrity of this nation's prescription drug supply and to reiterate our long standing commitment to doing our part.

In my testimony, I want to make several key points.

First, changes to the FDA Foreign Inspection process must recognize that the U.S. generic pharmaceutical review and approval system is very sound and is not broken, and that any modifications to Foreign Inspections must be undertaken in a manner that ensures a fair and level playing field. As a trusted pharmaceutical company, Barr, as well as all of the members of the generic pharmaceutical industry, are committed to ensuring that only the highest quality products, approved by the FDA, reach American consumers. We must meet very exacting product manufacturing and testing standards to ensure this and we hold our suppliers and active pharmaceutical ingredient suppliers to very exacting standards. We are perhaps the most highly regulated aspect of the current system, from the FDA requirements related to product development, application filing, final approval and post-marketing surveillance.

Second, while we applaud the FDA's ongoing efforts to remove unapproved products from the market, additional measures must be taken to prevent all counterfeit and unapproved products from being marketed to U.S. consumers and placing them at risk. This situation is untenable and must be addressed. We have several proposals to offer to assist this committee, and the FDA, in closing these gaps.

Third, we must meet very exacting product manufacturing and testing standards to ensure this. We are committed to working with this committee, as well as all members of Congress and the FDA, to implement needed and appropriate changes that will result in a system that treats all manufacturers, and all parts of the pharmaceutical supply chain, equally with respect to the integrity of all medicines.

Changes to the FDA Foreign Inspection process must recognize that the domestic system we adhere to is the best in the world and that any modifications must ensure a fair and level playing field with the goal of ensuring access, safety and efficacy.

We support the goal to give FDA adequate resources to test products, inspect facilities and perform the requisite oversight of foreign finished dosage forms and API manufacturers. I want to state for the record, however obvious, that quality cannot be tested into the product at the border. Foreign inspection must be as inclusive and robust as the strictly controlled processes that FDA requires of domestic manufacturers, including the assurance that products are made in facilities that have the proper core competencies, laboratories, and operational

manufacturing and quality systems to ensure total control over every facet of the development and manufacturing of every product we market.

BACKGROUND

Manufacturers of FDA-approved drug products operate in a highly regulated environment. FDA promulgates strict rules governing the development, manufacture, approval, packaging, marketing and post-marketing surveillance of prescription drugs. And to ensure the highest purity and quality, FDA has in place rigorous inspection standards for facilities that manufacture and supply prescription drugs.

While these stringent regulations apply equally to all brand, generic and biological prescription drugs approved by the FDA, there are drugs sold today in the U.S. without FDA's approval. These unapproved and unregulated products include, but are not limited to, counterfeit drugs and certain prescription drugs sold over the internet.

As this Committee knows, federal law requires that generic drugs have the same active ingredients, same dosage form, same standards for purity and quality,

same standards for manufacturing, and same amount of medicine absorbed into the body over the same time as the equivalent brand product.

In other words, to receive FDA approval, the FDA-approved generic must perform in the patient in the same manner as the innovator drug. This means the same amount of active ingredient must reach the bloodstream in the same time as the brand, and must remain in the bloodstream for the same length of time as the brand. While generics may occasionally be a slightly different size, shape or color than their brand counterparts to avoid trade-dress issues, these cosmetic differences have no impact on the safety or effectiveness of a generic prescription drug.

As the CEO of a company that manufactures both brand and generic prescription drugs, I can attest that the approval process for generics is equally as rigorous as it is for brand drugs. I can say further that all prescription drug manufacturers, both brand and generic, expend considerable resources for self-policing their operations through the auditing of vendors, testing of incoming materials, and completing quality programs in order to comply with FDA regulations.

The penalties for non-compliance are significant. Here in the U.S., CEOs and other senior management can be held criminally liable for any misconduct related to manufacturing prescription drugs. In addition, non-compliance can result in business interruptions that can cost tens of millions of dollars in earnings and can severely damage reputations.

INSPECTIONS

The Federal Food, Drug and Cosmetic Act (FDCA) requires FDA to conduct Current Good Manufacturing Practice (cGMP) inspections of all domestic prescription drug manufacturing sites every two (2) years. CGMP inspections provide the assurance that each product we market has the same quality, strength and purity as the product approved by FDA and that it is manufactured and tested in accordance to exact FDA-approved methods and standards.

In addition, in our highly regulated sector, there are also pre-approval product inspections for both brand and generic products – products that are subject to abbreviated or new drug applications. And there are the unannounced, periodic inspections to ensure companies continually remain cGMP compliant, and these

inspections can take anywhere from several weeks to months. Inspections are a vital component of the regulations that govern the brand and generic industries.

Unfortunately, FDA faces the serious challenge of having severely limited resources to undertake the much needed inspections of foreign facilities that manufacture finished dose and active pharmaceutical ingredients supplied to the U.S. market. Recent data presented by the FDA shows that while the number of foreign sites exporting pharmaceutical products to the U.S. has increased dramatically over the past decade, the number of FDA inspections of these sites has declined.[1]

For instance, in 2000 there were 1,436 cGMP inspections of domestic drug manufacturers and 248 foreign inspections. By 2004, the number of domestic inspections had risen to 1,825, but the number of foreign inspections had dropped to 184.[2] These data are more striking when considering that, in 2004, there were 2,700 foreign drug manufacturers registered with the FDA, compared to 3,300 registered domestic manufacturers.[3]

[1] FDA Perspective: High Priority Topics & Future Directions, Deborah Autor, Director, CDER Office of Compliance, October 10, 2007.
[2] CDER Reports to the Nation, 2004.
[3] Citizen Petition, Synthetic Organic Chemical Manufacturers Association, January 24, 2006, pg. 2.

In direct contrast to domestic inspections, foreign inspections are generally announced to the company many weeks, if not months, prior to that inspection, and only last for three (3) to five (5) days, with little to no follow-up inspections. By comparison, domestic inspections are unannounced, and frequently last longer than 5 days -- many routine domestic inspections can last for weeks.

A significant cause for the inadequate foreign inspection rate is that the U.S. has no statutory requirement that overseas plants be inspected. Further, FDA has no jurisdiction over foreign facilities. The FDA just does not have the manpower or financial resources needed to conduct even a reasonable number of foreign inspections. Indeed, FDA Deputy Commissioner Randall Lutter, in September testimony to the Committee on Energy and Commerce, remarked that some foreign companies that export medicines to the U.S. have not been inspected by the FDA in as many as 10 years. Furthermore, FDA has no inspectors permanently dispatched to India and China, despite these nations' rapidly expanding pharmaceutical industries. And lastly, when foreign facilities do get inspected, the outstanding question is whether FDA applies a lesser cGMP standard to those facilities than to domestics.[4]

[4] See 1993 FDA internal memorandum and 1998 GAO report.

This imbalance between domestic and foreign inspections creates a potential competitive advantage for manufacturers operating overseas where inspections are less frequent and liability less risky. Therefore, leveling the playing field in terms of domestic and foreign inspections should be one of the objectives as we move forward with this effort.

FDA APPROVAL OF RAW MATERIALS USED IN GENERIC APPLICATIONS

A critical component of generic pharmaceutical development, approval and marketing in the United States is the sourcing of the active pharmaceutical ingredient in the generic product. Here, ensuring that the source of the API can provide an approvable, reliable source of active ingredient is critical to success for the generic pharmaceutical manufacturer.

GMP compliance of the API manufacturer is critical. If a GMP deficiency is found at the API manufacturer, the approval of a generic product is delayed. Frequently, a generic manufacturer in the U.S. will invest in the processes necessary to ensure GMP compliance in its API suppliers. However, the API supplier must be GMP compliant before production can begin on the active

pharmaceutical ingredient that is to be included in the generic company's application for approval with the FDA.

Once GMP compliance is assured, the generic pharmaceutical company analytical research scientists analyze incoming materials to ensure that current and future supplies will consistently comply with quality requirements, including stability and process requirements. Sophisticated analytical methods are developed and implemented to ensure purity and quality. All of these sophisticated, scientific requirements become part of the Drug Master File, referenced in the generic application. This ensures the quality and purity of the active pharmaceutical ingredient in FDA-approved generic drugs.

U.S. GENERIC PHARMACEUTICAL COMPANIES SELF-POLICE THEIR PROCESSES AND PRODUCTS

In addition to FDA and numerous other regulatory requirements, generic manufacturers invest heavily in self-policing the sources of material and processes used. To assure the purity of the active and other ingredients, generic pharmaceutical manufacturers extensively conduct due diligence throughout the supply chain. The industry audits vendors to assure the quality and purity of all

active ingredients and other raw materials used in its manufacturing of prescription pharmaceutical products, including rigorous testing of incoming materials and assuring purity with Certificates of Analyses.

I strongly urge Congress to recognize the need to increase foreign inspection resources without cannibalizing the inspection of the generic pharmaceutical API supply chain.

While the generic prescription pharmaceutical industry takes extensive steps to ensure that our source materials and finished drug products are of the highest quality and are safe and effective for their intended use, FDA can and should supplement our actions with routine compliance inspections to: (1) validate our determinations of suppliers' compliance; (2) shore up potential missed system deficiencies; (3) facilitate pre-approval product inspections in a timely manner.

RECOMMENDATIONS

We recognize the risk of foreign-made, inadequately inspected, active chemical ingredients and finish dose drugs being introduced into the American supply chain. We support the laudable goal and underlying tenets of Congressman Dingell's Food and Drug Import Safety Act of 2007, H.R.3610. To this end, we

strongly support providing substantial funding to FDA's foreign inspection program, to ensure that FDA's quality standard is the world's gold standard. But we respectfully remind this subcommittee that any initiatives designed to improve the quality of products purchased by consumers must balance the benefits of the current processes under which America's generic pharmaceutical industry has built a bond of trust and service to consumers.

Modifications that would disproportionately place the burden on the generic pharmaceutical sector, such as the import line item fee or any other measure that would negatively impact the ability of companies to source high quality raw materials, could have negative consequences to our industry's ability to get new, affordable, FDA-approved generic products to market on a timely basis.

As I previously stated, while we believe that our FDA-approved prescription products adhere to the highest quality standards in the world, there is room for significant improvement in FDA's foreign inspection program. Our recommendations for improvements are as follows:

1. The consideration of new funding sources, including discussion of the value of potential user fees applied broadly and fairly. Such a system, if carefully

crafted and implemented, could ensure that FDA has the requisite resources to conduct cGMP and pre-approval foreign inspections of foreign facilities to the same extent and same rate and to the same standard as that of domestic companies.

2. The consideration of a DMF Type II: API user fee or API establishment fee to ensure that FDA has the necessary resources to conduct inspections of API suppliers. Under this proposal, the user fee could be a source of funding for increasing the foreign inspection safety net, with companies forfeiting a portion of their user fee if a DMF application was found to be materially deficient. Additionally, the allocation of a payment as part of a separate user fee structure would ensure that FDA had sufficient funds to inspect all entities in the business of APIs as well as finished prescription drug products, and would further motivate API manufacturers to ensure the quality of API and other raw materials targeted for the United States.

3. We also would propose that in the interim, FDA continue to implement a Risk Based Inspection System for better allocation of currently scarce resources, based on both the portfolio of products produced and the record of compliance. Under this system, FDA would concentrate efforts on

inspections of companies producing complex products, as well as records of compliance. Companies with strong records of compliance and positive inspections would be permitted to proceed to market with their products in the U.S. based upon this track record, without delays resulting from waiting for FDA pre-approval or surveillance inspections on every product. At the same time, this system would ensure that questionable or problematic facilities receive a comprehensive review and evaluation.

SUMMARY

America's generic pharmaceutical companies have a legal responsibility to ensure that our products are of the highest quality and are safe and effective. If we did not meet the rigorous requirements imposed by the FDA, our products could not receive approval and could not reach consumers.

As a result of FDA regulations, the generic pharmaceutical supply chain is perhaps the most rigorously tested process in product manufacturing in the world. In addition, we also have a fiduciary responsibility to our shareholders and a commitment to the public trust. That is why, in addition to the layers of specifications we meet for FDA approval, we are also committed to comprehensive internal auditing, evaluation, testing and due diligence programs to ensure that all

materials, including the active ingredients, are being procured from cGMP compliant facilities and meet FDA and our standards.

We are also consumers. And we fully recognize the need for increasing FDA inspection of products that are arriving in the United States, and are used by all consumers, that do not have the same hurdles to overcome as generic medicines. As an industry, we are committed to working with Congress to ensure that FDA has adequate resources to conduct foreign inspections that ensure not only the quality of our products, but of foreign-produced products as well.

In making this commitment to Congress, we are cognizant of the fact that balancing these competing demands for resources from FDA foreign inspectors could place the timely availability of U.S. generic pharmaceuticals at risk for delays. Therefore, our recommendations clearly support initiatives that recognize the rigorous nature of the regulations that we must meet, but also the need to formulate solutions that do not unintentionally damage our ability to supply high quality, effective and less costly medicine to consumers in a timely manner.

We seek to ensure that any modifications to the Foreign Inspection Process recognize the efforts expended by the generic pharmaceutical industry, and the

assurance of this committee that any modifications to the system will treat all manufacturers and all parts of the process equally. Failure to infuse adequate resources and implement reform measures will perpetuate a system where there is one standard for domestic FDA-approved prescription drug manufacturers and a lesser standard for foreign manufacturers. Our Foreign Inspection Process is only as strong as its weakest link, and we encourage this committee to focus on those areas where gaps of resources currently permit unapproved and unregulated products, including counterfeit drugs, to reach consumers.

Thank you. I would be happy to address any questions of the Committee members.

Mr. STUPAK. Thank you, Mr. Downey.

Mr. Villax, I understand you came from Europe to be with us, and we appreciate that. Thanks for being here, and we look forward to your testimony. If you would begin, please. Make sure your mike is on.

TESTIMONY OF GUIDO VILLAX, IMMEDIATE PAST CHAIRMAN, PHARMACEUTICALS BUSINESS COMMITTEE, MEMBER OF THE BOARD OF DIRECTORS, EUROPEAN FINE CHEMICALS GROUP, BRUSSELS, BELGIUM

Mr. VILLAX. Thank you. Good afternoon, Chairman Stupak, Ranking Member Whitfield, and members of the House Subcommittee on Oversight and Investigations. Thank you for inviting the European API industry to testify on the FDA's foreign inspection program. I am here in representation of the European Fine Chemicals Group. I am Guido Villax, chief executive of Hovione, a producer of APIs based in Portugal, present in China and in the U.S.A. Hovione was founded by my father 50 years ago, so it has been about 40 years that I have had a front seat watching changes in the pharmaceutical industry.

The European Union, like the U.S.A., has rules in place to assure that the active pharmaceutical ingredients used to make medicines meet cGMPs to assure that each medicine is identical to the product approved by the health authorities. Last century, medicines were either patented or branded and were manufactured mostly in the West, in-house, and in compliance with GMPs.

The world has changed. Today, driven by the demand globally for lower healthcare costs, off-patent medicines make up the majority of pharmaceuticals we consume. 80 percent of the API volume used to make EU medicines comes from abroad, and not everyone is playing by the rules. This is putting the safety of our citizens at risk. Globalization has resulted in the emergence of off-patent API production in the low-cost economies where regulations and GMP requirements are very limited compared to those in the EU. More complex and fragmented supply chains increase the potential for contamination, mislabeling, or substitution of one substance for another, all of which increases the risk to patients.

Unprecedented pressure on prices and profit margins drive generic and OTC companies to buy formulations and APIs at the lowest cost, sometimes from API plants that have never been inspected by any health authority from the EU or the U.S. This pits quality and ethics against profits, in an uneven fight. Without enforcement, the least scrupulous operator wins. In this new world, the West no longer produces the antibiotics that fight anthrax. The compliant industry has to meet ever growing, tougher regulations that add 25 percent to the cost. This makes cGMP-compliant plants uncompetitive versus non-compliant ones.

The EU regulatory framework has not kept pace with these dramatic changes. The lack of effective oversight, inspection, and no enforcement by the authorities has encouraged non-compliant, illegal trade, including the importation of APIs into the EU, mainly from Asia, via certain brokers and traders. This allows them to offer lower prices from a non-compliant cost base and to import substandard, often counterfeit APIs with a low chance of being

caught. Oddly, the EU inspects API plants based on proximity, not risk. In a year, European authorities may inspect 30 to 50 API plants in Asia, when Italy or France inspect a greater number in their own country alone. The few foreign inspections by the European Directorate of Quality of Medicines, EDQM, tell us something is broken. All the suspended approvals resulting from inspections were related to production in Asia. None were in the EU. All approvals that were withdrawn by EDQM related to filings in the name of middlemen. Some of the suspended approvals are of APIs for old OTC drugs that could well be exported to the U.S.A. and those facilities FDA would not have inspected. Some of the suspended approvals and FDA warning letters seem to be related to API producers that receive support from middlemen.

Last month, EFCG asked the European Commission to improve the oversight and enforcement of the regulations for APIs by increasing inspection resources and enforcement sanctions by adopting some of the systems that the U.S. FDA has in place and that here have been quite strongly criticized, but I would like to emphasize that we don't even have those in Europe. And the last thing we recommended to the European Commission is that they should take the leadership to regular middlemen and to seek international cooperation between agencies around the world.

Several supranational bodies, the European Parliament, the USP, and the WHO have recently recognized that more inspections are key to stop non-compliant APIs from reaching the market. Unscrupulous players cannot be allowed to take advantage of uncoordinated jurisdictions that allow them to escape by crossing the State line. The generics and the OTC medicines that the world needs cannot continue to be regulated by 20th-century structures and resources. The answer lies in more, but especially smarter, enforcement and the global cooperation of national medicines agencies. Thank you.

[The prepared statement of Mr. Villax follows:]

STATEMENT OF GUIDO VILLAX

Enforcing the Quality of Medicines in a New World Order

The European Union (EU) and the United States of America (US) have rules in place to ensure the Active Pharmaceutical Ingredients (APIs) used to make medicines meet current Good Manufacturing Practices (cGMPs). Compliance with cGMPs is what ensures that each pill and medicated syrup we consume, each injection given to us, and each IV administered to us has the same identity and strength and the same quality and purity characteristics as the product approved by the Health Authorities in the EU Member States and in the US.

However, not everyone is playing according to the rules, and the European and American public are being put at risk in two critical areas: patient safety and regional/national security. This is a consequence of the huge changes in the pharmaceuticals market over the past 20-30 years, due to globalisation and the internationalisation of the supply chain.

We face a new world order

An analysis of the major market changes over the last 20-30 years shows:

- The break-up of the innovator-dominated, pharmaceutical value chain
- The rapid growth in the off-patent (generics and over the counter (OTC)) market driven by the demand for lower health care costs by national health service providers serving an ageing EU population during a period of relatively low economic growth
- Companies that neither produce the formulated medicines nor make the API now supply the majority of generic medicines that now fill 60%[1] of the prescriptions in the USA.
- Patent legislation differences, globalization of know-how and free trade has led to the emergence of the production of off-patent APIs in the low cost economies, especially in Asia, where regulations and GMP requirements are still very limited as compared to EU legal requirements.
- Today around 80% of the volume of APIs that are used to make medicines found in EU and US pharmacies come from abroad.[2,3] A large and increasing proportion now comes from countries in Asia, up from close to zero 20 years ago.[4]
- Higher operating costs in GMP-compliant API manufacture in Europe, coupled with a dramatic increase in additional, industry-related EU regulations, has made Europe, once the cradle of the pharmaceutical industry, increasingly uncompetitive to produce off-patent APIs. This is causing the centre of gravity EU off-patent API manufacturers to be pushed out of their home market by competition from Asia
- EU law now requires a Qualified Person employed by a pharmaceutical company to assure the quality and compliance of APIs used in every batch of its medicines before sale. This requires back-up documentation and audit activities proving that the regulations governing its production have been met in full, including the use of GMP-compliant APIs.

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1 David B. Snow Jr., Maximizing generic utilisation: The power of pharmacy benefit management. Journal of Generic Medicines, page 28, October 2007.

2 Presentation by Jurgen Hoose, Authority for Science and Health, Hamburg, to the 7th APIC/CEFIC European Conference on APIs, Lisbon 20-22 October 2004.

3 EMEA has stated ...approximately 80% of active substances used in the manufacture of medicinal products within the EEA are manufactured outside of the EEA... in Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials (page 60/101 of Compilation of Community procedures on inspections and exchange of information. http://www.emea.eu.int/Inspections/docs/335103en.doc

4 See "The World API's market" publication by Dr. Giuseppe Tamburini, Milan, July 2005.

During this time, the volume and type of EU legislation, regulations and guidelines applying to the manufacturers of APIs and intermediates have increased dramatically. Today the API industry is being regulated to a level similar to the downstream pharmaceutical industry that manufactures final medicinal products.

API manufacture is today almost as strictly regulated as the manufacture of medicinal products. A large proportion of the pharmaceutical regulation in place does not take into account the existence of a separate highly regulated API industry. This means that compliance with API regulations and procedures is proving difficult and unworkable at times. Today, dedicated, specialised companies all over the world who serve as suppliers to manufacturers of medicinal products manufacture many APIs.

Applying cGMPs in an industrial setting is complex and expensive. It requires depth and breadth of knowledge and training, plus a great deal of discipline and time. Not meeting cGMPs enables savings that have been estimated at 25% of operating costs (excluding raw materials).[5] Compared to EU domestic facilities, uneven enforcement in foreign facilities means these sites can offer lower cost APIs with only a 'voluntary' regard for expensive cGMPs. Paying only cursory attention to cGMPs also allows for greater operational flexibility and faster product development which is decisive factor in the generics business where the first approval takes all the profits and remains with an enduring market share.[6]

The vast majority of medicines are no longer produced by the large multinationals; rather they are products whose patents have expired (generics) and medicines not requiring prescriptions (over the counter drugs or OTCs) that are supplied by a multitude of companies that very often do not make their own APIs but instead buy them from another company – who may just be a middleman.[7]

To illustrate the rapidly changing market, the number of ANDAs (Abbreviated New Drug Application) filed with the FDA in 2005 and 2006 is two and a half times greater than it was from 1994-2004 – and in last 18 months there were 36 new firms applying for ANDAs for the first time ever.[8]

Globalisation has caused unprecedented pressure on prices and profit margins and has driven these generic and OTC companies to buy their APIs at the lowest cost from plants that have never been inspected by any health authority from the EU or the US. In 2005, China alone – including European owned sites there – exported 39,700 metric tonnes of paracetamol; a 21% increase over 2004 and enough to produce billions of tablets.[9]

Globalisation has resulted in more complex supply chains, which increase the potential for contamination, mislabelling, or substitution of one substance for another, all of which increases the risk

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5 'Managing the Cost of Compliance in Pharmaceutical Operations'; Frances Bruttin & Dr. Doug Dean / IBM Business Consulting Services, April 2004.

6 "...in the US Hovione and its customers also lost millions of dollars in sales because Opos-supplied generic firms got their approvals first. " January/February 2005 Speciality Chemicals Magazine, page 4, Viewpoint – A Level Playing Field, Guy Villax, CEO of Hovione, calls on the European authorities to inspect API producers abroad.

7 Former FDA Commissioner, Dr. Mark McClellan, a strong advocate for generic drugs, in remarks before the First International Colloquium on Generic Medicine on September 25, 2003, said, "Generic drugs now account for the majority of prescriptions in the U.S., and the U.S. has some of the lowest-priced, safe generic drugs available anywhere in the world." He went on to say, "As nations are working hard to find ways to tighten price regulations and shift costs elsewhere, we run a serious risk if product developers don't think they can get a fair payment when they succeed. They will stop trying. They'll turn to products where the prices aren't regulated, like erectile dysfunction drugs and other lifestyle drugs."

8 Tommy Erdei, UBS, strategic considerations within the API sector, presented at APIs Europe 2007, Stresa – Aschimfarma and CPA.

9 Reference: "Chinese Paracetamol Export Business Analysis in 2005" by Chinese Medical Export/Import Association, No. 2006-1.

to patients.[10] Profit pressures in the generic and OTC medicines businesses pit quality assurance departments against the purchasing departments in the same company in an uneven fight. In absence of a referee, there is a predictable winner; the least scrupulous operator.

Because the EU regulatory framework is now out of date, the authorities cannot adequately deal with the effects of these changes in the EU API industry. The regulators are struggling to cope but the system is obstructing their efforts. This situation has increased the risk of non-compliance remaining undetected in API manufacturing and in the pharmaceuticals' supply chain, leading to detrimental effects on the health of EU citizens and on the competitiveness of the EU API industry.

The little evidence that we have shows overwhelmingly that the EU system is broken and that using short cuts has become a profitable business practice. All the 20 CEPs (Certificates of Suitability, the EU alternatives to DMFs for compendial APIs) hitherto suspended and withdrawn by EDQM were related to producers located in Asia, and about half of them were filings held in the name of "middlemen", i.e. filings not held by the API producer itself. Non-compliant producers were only identified when inspections were performed and too few inspections are performed in the region that seems to have more problems. It is interesting to note that EU inspectors have looked at API plants that produce the very products that FDA does not include in its enforcement roster (the older OTC drugs) and interestingly it has suspended CEPs for such drugs making them barred from Europe but nothing stops them from becoming a US medicine.

Consequences of the new world order

The consequences of all the above-mentioned changes are undermining the quality and safety of medicines in Europe, are creating a non-level playing field for EU API manufacturers by lowering their ability to compete, are acting as a barrier to innovation to improve competitiveness and are detrimental to improving protection of both the environment and the safety of workers in API factories.

These changes are working strongly against the European Commission achieving its two key objectives -to better protect the health of EU citizens and to strengthen the competitiveness of European companies- that EFCG strongly supports.

The EU regulatory framework, which affects the full length of the supply chain - from intermediates to APIs to formulated medicines - has not kept pace with these dramatic changes in the marketplace. Much of the EU pharmaceutical regulation now in place essentially ignores the existence of the separate, but now highly regulated, upstream API industry. As a result, compliance with API regulations and procedures are proving disproportionately difficult if not unworkable at times. This must be corrected as the consequences are having a detrimental effect on EU manufacturers of APIs and intermediates and on the health of its citizens.

The lack of effective oversight, inspection and law enforcement by the authorities has encouraged non-compliant, illegal trade, especially involving the importation of APIs into the EU - mainly from Asia - via certain brokers and traders. This is due not only to their ability to offer lower prices from a lower, non-compliant cost base, but also the opportunity to import sub-standard (counterfeit) APIs with a low chance of being caught.

Failure by the authorities to reverse this trend will encourage more of the EU-based players in the pharmaceutical supply chain to move to non-EU countries, taking with them many skilled jobs, sources of income and taxes and opportunities for investment.

Customers in the EU (and the US) may benefit from global competition in terms of cost of medicines but maintaining a minimum level of industrial capacity in key areas is essential to regional and national security. Pharmaceutical production capacity is a key issue from a security standpoint and we urge that

[10] DeSorbo, MA. Balancing Act. Pharmaceutical Formulation and Quality. 8(2) 2006: 22-24.

steps be taken to stem the loss of domestic API manufacturing facilities. Requiring that foreign facilities meet the same quality standards as EU (and US) plants will not, in and of itself, assure that regional and national security is maintained. However, rigorous enforcement of the same standards across all pharmaceutical productions venues will at least slow the departure to areas where a lack of enforcement results in lower costs of doing business and a higher risk to the health and safety of EU (and US) citizens.

EFCG feels that the EU competent authorities need to accept the existence of a new world order affecting the global pharmaceutical cluster and that they should therefore create a tailored regulatory framework for the full length of the pharmaceuticals supply chain, including APIs and their intermediates suitable for the 21st Century.

Proposals for the transition step

As a transitory step, the EU authorities must provide sufficient regulatory resources to effectively enforce the present regulations in the short term, and to fully enforce a new, integrated regulatory framework in the medium to long term.

The new regulatory framework must enable the delivery of a more effective and efficient public service than exists at present and be driven by the need to meet the Commission's twin objectives of (1) better protection of the health of EU citizens and (2) strengthen the competitiveness of EU companies by removing regulatory and non-regulatory barriers, which stifle innovation and impede access to foreign markets.

Unless these actions are taken, the EU-compliant, API manufacturing industry of the pharmaceutical cluster will be forced to exit serving the off-patent (generics) industry, and will focus on only serving the US market and the global Innovators.

During the transition step and to help deal with the design a new framework, EFCG has recommended to the European Commission that actions be taken to improve the Variation Regulations and the levels and focus of inspection and enforcement of the laws governing cGMPs.

Variations Regulations

The EU Variations Regulations are causing serious problems for the dedicated API industry. Current regulation requires most changes to API manufacture to be separately assessed by the authorities for each resulting medicinal product. At best, when just a few parties are involved, this introduces delays and costs into the process. However, one change in an API operation may often trigger the need for in total up to many hundreds of Variations to be submitted by the pharmaceutical companies for all their various Marketing Authorisation Applications. Clearly, such situations are unworkable. Ethical API companies will decide not to implement the change, whereas those with lower ethical standards will probably make the change without notifying customers or authorities.

The challenge is to define a new regulatory approach for APIs to both foster innovation in API manufacture and to maintain or improve the safety of medicines. EFCG sees 3 options:

1. The separate authorisation of APIs. This would solve all procedural problems.
2. A shift from inspection of post-approval documents to on-site inspections. If both customer and supplier apply modern quality management systems, the management of change will be secure. In "API to multi-customer" situations, this shift implies change management at multiple interfaces - a difficult task but feasible and more workable compared to oversight based on a full assessment of regulatory submissions.
3. Introduction of the concept of 'Quality by Design' to the pharmaceutical manufacturing and legislation process based on the principles of enhanced process understanding and strict process control. These principles have been accepted into policy by the FDA and EMEA but

are not yet adequately translated into practice at the approval level for new product registrations never mind Variations.

We believe that all these approaches would deter those who might be tempted to choose not to notify any changes in API manufacture and, therefore, should improve the safety of EU medicines.

The current rigor of control in Variations is grossly ineffective as there is seldom any check by EU inspectors that GMP operations are also regulatory compliant, and that what is carried out in the factory truly reflects the information on file that led to approval. Compliant firms are again disadvantaged compared to those who do not respect change control requirements.

Inspection and Enforcement

EFCG believes that the present strict API regulatory framework requires a robust system of inspection and enforcement with tangible sanctions (to act as an effective deterrent) for those companies that are out of compliance. Respected market analysts recently estimated the cost of compliance as being in the region of 25% of site operating costs[11] (excluding raw materials). The juxtaposition of these costs with the competitive advantage of non-compliance (facilitated by the lack of adequate inspections) leads to the only logical conclusion that inspection should be (as with final medicinal products) an integral part of the API regulatory process.

EFCG believes that the FDA has led the world in developing cGMPs that assure the quality of APIs. It is because of the FDA's enforcement activities that Europe was able to progress up the learning curve and become not only the home to the largest number of compliant API producers, but also the major contributor to the body of knowledge on cGMPs and compliant manufacture of APIs.

Many EU-based API manufacturers have been inspected by the US FDA and in some EU Member States, also by their own national authorities. However, in many other parts of the world where API inspection and enforcement have been largely absent, there is no incentive for manufacturers to incur significant extra costs necessary to meet cGMPs. The problem seems even more serious than 'mere' non-compliance with GMP. It appears that even companies in China and India that have been blacklisted by Nigeria's health authorities NAFDAC[12] because of their proven, deep involvement in exporting counterfeit medicines to that country, are still freely exporting APIs to the EU. Thus, the health of EU citizens is put at risk from sub-standard medicines. EFCG has noted that the FDA had issued Warning Letters to some of the leading firms in China.[13] Is this the tip of the iceberg? Are fast growth and compliance difficult to reconcile? Whatever the answer, increased patient risk should never be a consequence of financial success.

Unlike in the FDA, the EU authorities are unable to say exactly how many factories supply the APIs used to make its medicines. The European Directorate arranges most of the API inspections performed by EU officials abroad for the Quality of Medicines (EDQM).[14] In the 7 years that their inspection scheme has been in operation, around 80 API manufacturing sites were inspected with about half in India and China. These inspections yielded 20 suspensions of the Certificates of Suitability (CEP) from 13 different holders that had been issued by the EDQM. All 20 suspended CEPs covered API

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11 'Managing the Cost of Compliance in Pharmaceutical Operations'; Frances Bruttin & Dr. Doug Dean / IBM Business Consulting Services, April 2004.

12 See http://www.nafdacnigeria.org/blacklisted.html.

13 See warning letters addressed to Wockhardt (February 21) and Ranbaxy (June 15) - CDER's 2006 warning letters under at http://www.accessdata.fda.gov/scripts/wlcfm/indexissuer.cfm.

14 The European Directorate for the Quality of Medicines (EDQM) is an institution of the Council of Europe. No other European Institution has done as much as the EDQM to start enforcing GMPs also at Asian producers of APIs.

manufacture in China or India. Those CEPs had been relied upon by the Medicines Agencies across the EU to approve medicines for sale,[15] but when they were suspended because of serious non-compliance no action was taken by the competent authorities – the EU medicines Agencies have no agreed procedure on how to act on such notification of suspensions.[16] None of the EDQM inspections performed in Europe led to a single CEP suspension.

At the last count, the EU probably performed more than 30 inspections outside the EU in the last 12 months. The FDA performs about 200 foreign inspections per year to API producers and maybe 10% are in Asia. As an illustration of the 2 countries that are doing their best to correct the lack of proportionality in the geography of inspections versus location of API production – note:

- The Italian health agency has currently 139 API producers GMP approved. It performed 86 inspections between February 2006 and September 2007. The agency has indicated that on average, it performs 48 inspections in Italy and 6 abroad – and it has issued 5 GMP certificates to API plants outside of the EU.
- The French Medicines' Agency performed a total of 77 inspections (in France: 8 distributors, 46 producers of which 1 covered excipients and the others APIs) – and abroad it performed 23 inspections (of which 9 with EDQM, 4 with the WHO and 4 with the EMEA).[17]

The continuing lack of adequate levels of inspection and enforcement will increase the risk of sub-standard (counterfeit) APIs entering the EU (and US) market from less ethical producers who, by avoiding these costs, enable unethical traders and brokers to supply APIs to pharmaceutical producers based at a much lower price than compliant producers. Not only should the new regulatory framework allow for the public punishment of those companies for whom non-compliance is at the heart of their business strategy, but also it should reward compliant firms with mechanisms for less intervention and faster approvals. Indeed, we recommend that inspection and enforcement of API laws should be performed along similar lines as for final medicines.

In an attempt to strengthen the rules affecting cGMP compliance for APIs, a majority of the Members of the European Parliament (MEPs) signed a Written Declaration[18] in November 2006 that informed the Council of Ministers, the EU Commission and the Member State Parliaments of the benefits to the EU citizens if (1) producers and importers of APIs to the EU were required to submit a certificate of GMP delivered by the EU authorities following mandatory inspection of the production site irrespective of its worldwide location, and (2) to introduce traceability of the API's country of origin via appropriate labelling of the final medicine in order to discourage re-labelling or repackaging of non-EC products in the interest of public health. The European Commission has informed the MEPs that it does not intend taken any action, instead waiting for the effect of recent regulatory changes to the law on GMP compliance for APIs to have sufficient elapsed time to allow for a proper assessment.

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15 Presentation by Head of EDQM Certification Unit (Corinne Pouget) at the EFCG conference, Barcelona 26- 27th April 2006, see www.efcg.cefic.org . EDQM has issued over 2000 Certificates of Suitability (CEPs), but has inspected no more than 80 producers.

16 EFCG's "Conclusions" on the Barcelona Conference, 27th – 28th April 2006, http://efcg.cefic.org.

17 Presentation by Lionel Viornery, AFSSAPS France, 2nd EFCG Conference, 24-25 May 2007, Berlin and Ana Rosa Marza, AIFA, "La Sicurezza del Fármaco nello scenario Europeo" APIs Europe 2007, Stresa, Aschimfarma and CPA.

18 European Parliament Written Declaration on pharmaceutical active principles No 0061/2006; DC\627587EN.doc

As recently as October 2007, EFCG has strongly recommended to the European Commission[19] the following actions to improve the oversight and enforcement of the regulations for APIs:

- increasing inspection resources and enforcement sanctions
- increased publicity of deterrents by the authorities
- creation of a central foreign inspection service for API producers to plan and coordinate non-EU inspections to ensure GMP and regulatory compliance by all non-EU producers that wish to export to the EU, and to uncover criminal activities such as fraud, counterfeiting and deliberate non-compliance.
- creation of a publicly available database of the results of inspections disclosing compliant and non-compliant producers
- creation of a supervised EU licensing system for brokers, traders and distributors
- creation of an API producers registration and identification system for use by EU Customs
- the personal legal liability of Qualified Persons to become law.

To help deal with the growing counterfeit problem, EFCG has also recommended to the European Commission that consideration be given to the setting up of a 'Global Regulatory Council' of the major nations to agree how to work together to minimise illegal behaviour in the production and supply of all medicines worldwide, and to ensure alignment and cooperation in the fight against deliberate non-compliance and counterfeiting. Perhaps such a body could be built either on the Pharmaceutical Inspections Cooperation Scheme and/or the WHO's recently announced procedure for assessing the acceptability, in principle, of APIs for use in pharmaceutical products.

As an interim measure, and to save EU resources, EFCG proposed a Mutual Recognition approach to provisional approval for those non-EU API manufacturers who have FDA and perhaps other mutually recognised approvals.

Conclusions

The United States Pharmacopeia[20], the PIC-S (Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme)[21] - which FDA has recently applied to join- and the World Health Organization all have started to face the inevitable: the imperative need to make sure non-compliant APIs are prevented from reaching the market. The need to establish some kind of inspection-based verification of compliance in API plants is now on everyone's 'To Do List'.

In a globalized world, in an industry with very international supply chains, unscrupulous players cannot be allowed to take advantage of uncoordinated jurisdictions that enables them to always find a safe haven by crossing the "state line". This new world order cannot be regulated by 20th Century structures and resources; the answer can only lie in global cooperation of all enforcement agencies.

Organisation

EFCG[22] represents the interests of over 100 fine chemical manufacturers who have plants, primarily located in Europe, but also in Asia and North America, producing APIs, intermediates and

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19 EFCG submission in response to the European Commission's consultation on 'The Future of Pharmaceuticals for Human Use in Europe' October 2007 see http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2007/2007_07/consultationpaper-2007-07-19.pdf and http://www.efcg.cefic.org/publications/items/2007-08.html

20 United States Pharmacopeia (USP) Verification Program for pharmaceutical Ingredients - see http://www.usp.org/USPVerified/pharmaceuticalIngredients/

21 Pharmaceutical Inspection Cooperation Scheme (PIC/S) – see http://www.picscheme.org/index.php

22 *The European Fine Chemicals Group*, a sector group of CEFIC – see www.efcg.cefic.org

pharmaceutical excipients serving worldwide customers in innovator, generic and OTC pharmaceutical companies. Western Europe produces over $12 billion of APIs.[23] A typical turnover for a member company is less than $200 million pa.

EFCG represents an industry that has supplied APIs to the USA for the past 40 years.

EFCG is a sector group within CEFIC – The European Chemical Industry Council - the international organisation that represents national federations, companies and more than 100 affiliated associations and sector groups located in Europe. With the help of CEFIC, EFCG - together with its sister organisation – the Active Pharmaceutical Ingredients Committee (APIC) - provides a forum on scientific, technological, regulatory and trade related issues in the area of active pharmaceutical ingredients, and organizes an effective flow of information among the members, drawing upon their expertise.

[23] See "The World API's market" publication by Dr. Giuseppe Tamburini, Milan, July 2005.

Mr. STUPAK. Thank you, Mr. Villax, for your testimony. I am going to start with questions. We will start with the chairman of the full committee, Mr. Dingell, for questions, please.

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy. Mr. Villax, yes or no, isn't it true that in some places like China and India basic clean water and sanitation are major problems?

Mr. VILLAX. I think that, absolutely, yes. However——

Mr. DINGELL. Doesn't this then mandate that a higher level of care with regard to products of those countries, especially with regard to inspection of plants there, should be one of the guidelines of the United States' policy with regard to imported foods and drugs?

Mr. VILLAX. China has made tremendous progress.

Mr. DINGELL. But the progress isn't enough. They have still got lots of dirty water, polluted air, major problems with sanitation and health over there. And doesn't require us to engage in much more careful inspection of products that are manufactured there? Yes or no.

Mr. VILLAX. Yes.

Mr. DINGELL. OK. And thank you for that. I don't mean to be discourteous, but I have got 5 minutes, 1 minute of which is now gone. Now, gentlemen, these questions. Dr. Dubeck, isn't it true that nearly half of all drugs marketed in the United States are produced or manufactured in foreign facilities and that that number is increasing?

Mr. DUBECK. Those are statistics from FDA and GAO, correct?

Mr. DINGELL. Isn't it a fact that cGMP inspections of foreign firms result in significantly higher violation levels than are seen in domestic firms?

Mr. DUBECK. That is what was reported at the Georgia GMP conference, correct?

Mr. DINGELL. Isn't it fair to say that foreign firms generally pose a greater risk with regard to quality and safety to consumers than do domestic firms?

Mr. DUBECK. I think that necessarily follows from the above.

Mr. DINGELL. Now, Mr. Downey, do you agree that the current imbalance between foreign and domestic inspections places U.S. domestic firms at a competitive disadvantage?

Mr. DOWNEY. In some ways, yes. Other ways, no.

Mr. DINGELL. In other words, we have got to meet high standards, and they don't.

Mr. DOWNEY. That is true, but it is also more difficult to get a pre-approval inspection for a product as a foreign manufacturer, so you are at a competitive disadvantage because you are inspected less frequently.

Mr. DINGELL. And they can slip bad stuff in here, and get away with it and American firms can't?

Mr. DOWNEY. I don't believe bad stuff is being slipped into the country. I don't think that is so.

Mr. DINGELL. Well, let us see about what the findings of this committee might be on that particular point. Now, do you think that it would be beneficial to have FDA open offices in those parts of the world that are significant exporters of production to the United States of prescription pharmaceuticals?

Mr. DOWNEY. I think there should be parity in inspections, and that is one way to increase the inspections in Asia. Yes, sir.

Mr. DINGELL. Now, Mr. Downey, isn't it true that if a facility is not inspected frequently, the safety of drugs coming from that plant could be affected?

Mr. DOWNEY. Could be, but not necessarily would be.

Mr. DINGELL. But there is a better chance if they are not inspected than if they are.

Mr. DOWNEY. The inspection of the facility is one component of a very comprehensive regulatory system, and——

Mr. DINGELL. And it encourages good behavior and a right conscience, does it not?

Mr. DOWNEY. I think responsibility of what we are doing encourages behavior, and that is the basis——

Mr. DINGELL. Now, isn't it fair to say that as long as FDA's foreign drug inspection program is so poorly funded and its IT systems in disarray that our medicine supply is at risk?

Mr. DOWNEY. I believe we need better foreign inspections, more resources in that area, yes.

Mr. DINGELL. Good. Mr. Villax, you had a comment.

Mr. VILLAX. Yes, I think that there has been a lot of emphasis that we need more inspections, and I agree, but the fundamental impact of inspections is deterrence, and this is what is needed. You ought not to have areas of the industry that get zero inspections. You ought to have them spread out and probable. That is what causes the drive for compliance, and this is where Europe is catastrophically weak.

Mr. DINGELL. Gentlemen, you can have inspections at the point of entry, you can inspect for efficacy and safety here, but you also have to inspect or you have to have knowledge of whether good manufacturing practices are carried forward in the country of origin, and also whether or not the different components that are exported here or the components that are included in that country are in fact safe. Is that not true?

Mr. VILLAX. In fact, you must absolutely check the process.

Mr. DINGELL. And not only the process but the components.

Mr. VILLAX. Well, I was talking from an API perspective. When you make the active ingredient, you obviously have some accepted sources or approved sources of raw materials, but you need to make sure that it is GMP compliant, and you need to make sure it is regulatory compliant. What I mean by this is that you have to check two things. One, that you follow good manufacturing practices.

Mr. DINGELL. Yes.

Mr. VILLAX. The other thing is that you need to do what you have put in your filing. In other words, the inspectors need to make sure that what is in the filing in Washington is the same thing that actually is taking place in the plant. Because that is the only way you can actually guarantee traceability and that what you did in your bioequivalence test remains the same thing year after year.

Mr. DINGELL. Gentlemen, I want to express my thanks to you. I apologize for being so brusque, but that clock is a harsh master. Thank you.

Mr. STUPAK. Now Mr. Whitfield, for questions.

Mr. WHITFIELD. Thank you, Mr. Chairman. Mr. Villax?

Mr. VILLAX. Villax.

Mr. WHITFIELD. Villax, OK. Now, my understanding, you are actually the chief executive officer of a company that makes medicine, correct?

Mr. VILLAX. We manufacture APIs, both for the generic industry and the innovator industry.

Mr. WHITFIELD. OK. And so you import into Portugal—is the plant in Portugal?

Mr. VILLAX. We manufacture in Portugal, and we had our first inspection by FDA in 1982 and export to the U.S. market. We also manufacture in Macao. It is in south China, and that, we had our first inspection there in 1987 and export into the U.S.A.

Mr. WHITFIELD. Now, tell me again. You alluded to this a little bit. How would you compare the European system with our U.S. system as far as maximizing the safety for the consumer?

Mr. VILLAX. Well, Europe has been late in bringing in systems that you have had for three, four, or five decades. Europe does not yet have a foreign inspection system, although the industry has been pushing them.

Mr. WHITFIELD. So Europe does not have any foreign inspection system?

Mr. VILLAX. Well, we don't have a foreign inspection system, but we have certain authorities around Europe that make a special effort to go abroad and check. We have especially something called the EDQM, the European Directorate for Quality of Medicines, that is associated to the European Pharmacopoeia, and they have been the agency that have tried hardest to go abroad. But I think the numbers that I have is that in 7 years they have done 80 inspections internationally, which is very small.

Mr. WHITFIELD. In 7 years. Wow. So I know it is difficult to summarize this, but as bad as our system is in the U.S., I mean with our shortcomings, I am going to say——

Mr. VILLAX. You are way ahead.

Mr. WHITFIELD. We are way ahead.

Mr. VILLAX. And you are the gold standard.

Mr. WHITFIELD. All right.

Mr. VILLAX. In other words, if GMPs were developed, with thanks to FDA, and Europe has been free riding on what FDA has been doing.

Mr. WHITFIELD. Really?

Mr. VILLAX. Absolutely.

Mr. WHITFIELD. So despite our shortcomings, we are the gold standard, and Europe has been free riding with us, then. That is good. Now, let me ask you, you discussed in your testimony some of the—no, actually it wasn't you. I guess it was Mr. Dubeck. You discussed in your testimony some of the risks presented by the fact that over-the-counter drugs are not subject to any pre-approval barriers, especially with regard, and I think you mentioned ibuprofen, and how would you propose that FDA remedy that problem?

Mr. DUBECK. Well, ibuprofen is currently a new drug and is under all of the inspection and reporting that Mr. Downey summarized. The FDA proposal is to make it a not-new drug. Once it does

that, all of the additional precautions that Mr. Downey mentioned disappear, and all you really have left is cGMP monitoring. So there needs to be the same level of inspection of OTC facilities because even though they may not have some of the same inherent risk as some very new prescription drugs, they are consumed by the public in much larger quantities.

Mr. WHITFIELD. Right.

Mr. DUBECK. And so impurities in those products wind up causing much greater exposure to the American public, and there is no inspection.

Mr. WHITFIELD. Which is hard to believe, really.

Mr. DUBECK. Our members that make these APIs and try to compete also find that hard to believe.

Mr. WHITFIELD. Now, the foreign establishments that produce these active pharmaceutical ingredients are not required by Federal Law to register with the FDA if their products are not directly imported into the U.S. Now, considering that more of these manufacturers are being outsourced, you would recommend that all the establishments be registered with the FDA?

Mr. DUBECK. If they are—I mean, under the Law, a drug includes finished-dosage form and components of drugs. The registration requirement includes APIs, so right now registration is required for all the API manufacturers.

Mr. WHITFIELD. Even if they are not directly imported into the U.S.?

Mr. DUBECK. No, only if they are imported into the United States.

Mr. WHITFIELD. OK. All right. Now, Mr. Villax, would you please describe the European Union Law that requires a qualified person employed by a drug company to assure the quality of APIs used in medicines?

Mr. VILLAX. Yes, this is a very recent legislation.

Mr. WHITFIELD. All right.

Mr. VILLAX. It came into force in October 2005, and what that legislation says is, first, it is based on the fact that we do have now as Law something that in the industry we refer to as in other words, there is well-defined law that defines what are GMPs, and the Law that came in, in 2005, states that the QP, the qualified person, that is, the person that releases batches of finished product in the marketplace, this person has to make sure that they only use APIs that meet GMP. So this is a bit of self-regulation. In other words, Europe doesn't really believe in inspections, I think wrongly, and what they are expecting is that the QP takes personal responsibility for checking that the APIs meet GMP, and how this QP is expected to meet these obligations is by developing a close relationship with the producer of API. Like Mr. Downey said, he has a team of six auditors that go round the world producing audits so that the QP is expected to have audit reports that satisfy him that the producer of the API meets the GMP.

Mr. WHITFIELD. And are there significant sanctions if a company improperly assures the quality of the API?

Mr. VILLAX. I have written a couple of articles that compare or that say that the liability of the QP is substantially lower than that of a CPA that signs off a balance sheet. In other words, share-

holders are better protected than patients, and one of the requests that we have made to the EU Commission is that they have to somehow come up with personal liability for the QPs, because otherwise we have the purchasing department fighting with the quality unit.

Mr. WHITFIELD. Right.

Mr. VILLAX. And we all know who is going to win.

Mr. WHITFIELD. Thank you very much.

Mr. STUPAK. Mr. Inslee, for questions.

Mr. INSLEE. Thank you. To put it in the vernacular of the peasantry, this is a fine kettle of fish that we have got. 80 percent of our active ingredients coming in from imports. It is doubling the amount every 5 years, and we find out we just don't have a meaningful inspection protocol. It is most troublesome, and I just want to ask if my understanding is correct that we are proposing that that actual situation is going to get worse. As I understand it, I am told that the full-time equivalents, the FTEs of the FDA's foreign inspection program, was 149 in 2002. By fiscal year 2008, the FDA estimates that number will actually drop to 102. Now, we have tried to remedy that in our budget by increasing some of these appropriations. The president has threatened to veto our budgets, didn't have a veto pen for the first 6 years of his presidency, and all of a sudden he wants to veto these budgets. My understanding is that essentially, even though we already have a pathetically indifferent system to these imports, they are wildly less protective of the American public than our domestic production. I am told we can't even find out who these manufacturers are to have a really good compilation of them. Even though we are already bad, we are going to get worse unless we can override this president's veto on these appropriations bills. Could you gentlemen help us in understanding if that is correct or not?

Mr. DOWNEY. I wouldn't agree with a good deal of your comments. I will say this, that we have 12 full-time auditors that audit our raw material suppliers, and we are a very small part of our drug supply system, so I think having 100 or 150 is definitely inadequate. But I don't agree——

Mr. INSLEE. I am sorry. Did you say inadequate?

Mr. DOWNEY. Absolutely, inadequate. I don't think you can properly fulfill the role that inspection plays in the overall regulatory process with that number of inspectors. I just don't think it can be done. But, on the other hand, I think we have in place a very large number of safeguards that I explained in my testimony that I think protect and ensure that we have high-quality, safe pharmaceuticals. I think the biggest risk are counterfeiters who don't register, don't subject themselves to inspection, and we really need to make sure that the first priority is allocating the resources to discover the people who are blatantly and in criminal violation of our statutes bringing products into the United States and supplement that with appropriate levels of inspection for those who are regulated.

Mr. INSLEE. Well, foreign field inspectors would help on the counterfeit problem, would they not, as well?

Mr. DOWNEY. I don't think they have a very large role in that at all.

Mr. INSLEE. OK. Well, let us talk about the first problem. I thought I heard Mr. Downey say that there is no legitimate reason to have a lesser standard of inspection for foreign manufacturers than for domestic manufacturers?

Mr. DOWNEY. I absolutely think that is true.

Mr. INSLEE. You totally agree with that? Well, if you look at the chart up here that I am holding, showing the FDA foreign field funding, you see a constant decline that we are trying to remedy in our appropriation that the president has threatened to veto. Now, I want to make sure that I understand your testimony. I thought you were telling us that you want, you thought we should have the same level of inspections——

Mr. DOWNEY. Absolutely.

Mr. INSLEE. For foreign productions as domestic. We are not doing that right now, and we have a decreasing number of people that are going to do that, so I would assume you agree with me that that is a bad state of affairs, and we should increase the number of inspections and we should override the president's veto if we have to, to get that done.

Mr. DOWNEY. I think we should increase the number of inspections. As I said, I think my recommendation would be that, starting tomorrow, you reallocate inspectors to the foreign inspections because relative to domestic inspections they are too infrequent, and simultaneously work to increase the resources to have enough inspectors to conduct the appropriate number of inspections of both.

Mr. INSLEE. Well, I think this hearing is instructive, because I think it is important for the American public to know that we have got a president who is threatening to veto a bill that will increase protections of Americans against foreign imports that do not meet accepted standards, and I am hoping this hearing can help remedy that situation. Thank you.

Mr. DOWNEY. I have very little power over the veto.

Mr. INSLEE. We have some. We might need a few more votes. If you have any friends, you might talk to them. Mr. Villax, did you want to say something?

Mr. VILLAX. Yes. The plants located abroad that make APIs find these inspections very important because it is tough to meet the requirements of an inspection, and we need these inspections to make sure we have a level playing field. And the members of our association, we have gone on record to say we are happy user fees for these inspections. These are important inspections to have.

Mr. INSLEE. Thank you. And when the EU gets a role in Congress we know you are going to help us override this veto.

Mr. VILLAX. Well, I think you should approach the EU and say that you want to set up some kind of, or FDA needs to agree with them, to recognize each other's inspection reports. This is what I meant by more smarter enforcement, because they do between 20 and 50 inspections in Asia.

Mr. INSLEE. I think that is an interesting proposal. Thank you.

Mr. STUPAK. Thank you, Mr. Inslee. Actually, that has been a proposal the committee has made to the FDA, that why don't we recognize the inspections that the EU may be making, provided your regulatory scheme, which is same or similar to the FDA? It doesn't make any sense for the EU to do one, and 6 months later

the FDA comes in. We could do that—Do you share information? Does the EU share information with the FDA? Let us say you go to a place, and you inspect, and you find a problem here. In this country we call them 483s, a violation on inspection. Do you share that information?

Mr. VILLAX. As I understand it, the Europeans approached FDA many years ago to do these memorandums, or these mutual recognitions, but since we didn't have a Law about what were the standards of GMPs, it never moved forward. And I think until such time as we have a foreign inspection program in Europe it won't work, because you can't talk to 27 agencies. You have to talk to a single one. Now, I understand that informally there is quite a bit of information that goes backwards and forwards.

Mr. STUPAK. Well, good, but do you agree you don't know what it would be on inspections of foreign plants?

Mr. VILLAX. This is very complicated, and it is very political.

Mr. STUPAK. I understand. The QP you talked about, this quality person within the plant, the company that is manufacturing the API, they are responsible for that individual?

Mr. VILLAX. No, no. No, the pharmaceutical company that makes the pills that go into the market——

Mr. STUPAK. But not the API?

Mr. VILLAX. The API company——

Mr. STUPAK. You don't have any QPs in your plant in Portugal.

Mr. VILLAX. Not for the role that you are describing.

Mr. STUPAK OK. So it is just the pharmaceutical that makes the finished product?

Mr. VILLAX. Yes.

Mr. STUPAK. And then that individual is responsible to make sure the ingredients, the API ingredients, going into the final product is——

Mr. VILLAX. Were made according to GMP, yes.

Mr. STUPAK. OK.

Mr. VILLAX. So that is why they audit.

Mr. STUPAK. And then that standard would be based upon the country in which they are shipping it to?

Mr. VILLAX. The GMP standards that have to be met and that the QP has to certify are the GMP standards of the market where the pills are going to be sold, and——

Mr. STUPAK. Correct.

Mr. VILLAX. In Europe we now have the same standards.

Mr. STUPAK. OK.

Mr. DUBECK. Chairman Stupak?

Mr. STUPAK. Yes, Mr. Dubeck.

Mr. DUBECK. I would like to comment that all the inspections that the U.S. pharmaceutical companies do of imported APIs do provide a high degree of quality assurance, and so the mere fact that APIs made overseas don't get inspected very much, that would include Mr. Villax's products, does not mean we don't have high confidence in them. You will see, however, that many more approval applications are now being filed by foreign companies, which means that what is coming in are finished-dosage forms, and you don't have the U.S. manufacturer analyzing, reanalyzing the API

and all the quality steps that have been described when it comes in as a finished-dosage form.

Mr. STUPAK. Well, my question is going to be, and I don't know if Mr. Downey or to you, Mr. Dubeck, if you have a quality person, you have the same thing at Barr Pharmaceuticals, I take it? Or not——

Mr. DOWNEY. In our European facilities, for products made for sale in Europe, they are released by the QP.

Mr. STUPAK. What about here in the United States then?

Mr. DOWNEY. Well, they are released by our quality control——

Mr. STUPAK. OK. Do you have any plants overseas and not in Europe, not in the United States?

Mr. DOWNEY. No, all of our plants are in—well, we have a plant in Croatia, which is not part of the EU, but it is European.

Mr. STUPAK. Do you have a quality person there?

Mr. DOWNEY. Yes, we have QPs. Actually, the QP for release into the EU is in our polish facility, because not only does the QP have to be there, but the actual release testing for the European Union must be done in a European Union country, and so our release testing for product made in Croatia is Poland.

Mr. STUPAK. OK. Well, let me ask you this question. Our committee staff was both in India and China during the August break to check on the manufacturing practices at some of the facilities over there. Our staff met with senior government and industry officials in India, and both expressed strong support to have the FDA locate a permanent office in India. China, we got just the opposite. We got a push-back about having permanent offices in China. Do you think it would be beneficial for the FDA to open offices in those parts of the world where significant drug production or APIs for the U.S. market is taking place?

Mr. DOWNEY. That is one way to address the need to have parity in inspection, is to have people on the ground. That would certainly reduce travel time, would probably be less expensive, and I would say that that reaction, I am not surprised, and I think the Indian pharmaceutical industry is more advanced in terms of its quality systems, its exposure to Western regulation, more modern regulation than our Chinese suppliers. So I am not at all surprised by that. In fact, I mentioned earlier, our Indian members of the GPhA complain that they can't get inspected fast enough for their new product approvals. As we mentioned earlier, there has to be an inspection prior to a new approval, and they can't get people on the ground there, and it is very frustrating to them.

Mr. STUPAK. Right, and the Indian government officials felt that if we had a permanent office there that those inspections would take place much quicker.

Mr. DOWNEY. It is certainly an idea that is worth exploring. I can't comment as to whether it is the right way or not.

Mr. STUPAK. Mr. Dubeck, would you care to comment?

Mr. DUBECK. I think it would make a whole lot of sense. If we have overseas U.S. personnel for Customs and Immigration and for USDA, it makes sense it should be there for FDA.

Mr. STUPAK. Well, let me ask you this, Mr. Dubeck. In your testimony, it says that cooperative arrangements with foreign governments to determine the safety of drugs for the U.S. market are,

and I quote now, "a poor substitute for a visit by the FDA". The FDA is currently negotiating a memorandum of agreement with China with regards to product safety. Are you saying that this type of arrangement won't protect the safety of the drugs as much as a FDA inspection of a plant in that country?

Mr. DUBECK. Correct. I mean, these memorandum provide for sharing of information, so that FDA would at least have access to whatever inspection reports the Chinese may conduct, but, as it has been commented, FDA is the gold standard. The FDA inspectors, when they get there, they do the best inspections, and so, I mean, that is part of the problem of relying upon inspections by other government agencies. They are not the same.

Mr. STUPAK. GAO indicated and also our staff has reported back that when you go to a foreign country, let us say like India or China, you are under a time limit of how much time you actually have, which is really counter-productive to— in the United States, if it takes a month, it takes a month. In foreign countries, if you only have 3 days, you get in what you can in 3 days.

Mr. DUBECK. Yes, and when it takes a month in the U.S., it is usually not a month, every single day of the month.

Mr. STUPAK. Right.

Mr. DUBECK. They come for a few days, they go back, they get caught up on their paperwork, then they come back, they may bring other people with them when they come back. And so it is much more conducive to doing a thorough, competent job than when you are on the road, going from hotel to hotel.

Mr. STUPAK. I agree. Mr. Villax, in discussions with committee staff, you expressed concern that the U.S. does not sufficiently inspect foreign production of over-the-counter medications or the ingredients that go into them. Why is this important? What dangers come from the failure to inspect this class of medicines?

Mr. VILLAX. I was referring very much to the issue that John Dubeck raised, and this is related to the older drugs that, as I understand it, are not in the realm of probability to be inspected, and I think that the deterrence factor of FDA inspections is the critical aspect and therefore every single drug establishment ought to have a probability of being inspected.

Mr. STUPAK. OK.

Mr. VILLAX. And if I could add something on the inspections.

Mr. STUPAK. Sure.

Mr. VILLAX. Inspections abroad and inspections in the U.S. are really very different. When FDA inspectors come to Hovione, we invite them, and they are pre-announced, and they do not last as long—it probably lasts 3 days or 5 days—but we have had inspectors that have changed plans because they wanted to stay longer. But they also start at 8 o'clock in the morning and probably stay until 7 o'clock in the evening, and one of the reasons why these inspections can go much faster is that in the U.S. inspection, they have to collect data and have proof in case they are taken to Court. In Europe, they have no need to collect proof because if they don't like it they pick up the telephone, they call Washington and say, tell Customs to hold everything from Hovione. And we can't take them to Court, so it is probably more effective and faster.

Mr. STUPAK. The unadulterated drug angle of it. OK.

Mr. DOWNEY. I would agree on that point that the problem is the frequency of inspection, not the quality of the inspection, at least as we experience it. I don't know about the language barrier so much in Asia, but in European inspections, I would say that they are quite comparable between the U.S. FDA inspections conducted there and those conducted here in our facilities.

Mr. VILLAX. One of the——

Mr. STUPAK. Well, that is one of the things that we are asking the GAO to follow up on, and then what happens to a 483 when it hits the FDA? What I understand, they are basically deep sixed. Nothing ever happens to them on a foreign one, so—well, those are things we are asking GAO to continue, and that is why Dr. Crosse and her group did a great job given what they had, but we are following up. Go ahead, Mr. Villax.

Mr. VILLAX. One of the benefits of having offices in India or China is to bridge the culture. The culture distance between the U.S. and Europe exists. But there is a much greater distance, and I think having inspectors that gain an understanding of these cultural differences is probably very helpful in an inspection.

Mr. STUPAK. Well, thank you, and thank you to this panel for your insight and your assistance on this problem that has been going on for some time. We are trying to address it. We appreciate you coming. Mr. Villax, thank you for coming over from Europe and sharing your insight on what you are doing in Europe. Mr. Downey, Mr. Dubeck, thank you. We will excuse this panel, and we will call up our third and final panel.

Our witness to come forward is the Honorable Dr. Andrew von Eschenbach, Commissioner of the Food and Drug Administration. Accompanying the Commissioner is Ms. Margaret Glavin, Associate Commissioner for Regulatory Affairs at the FDA. It is the policy of this subcommittee to take all testimony under oath. Please be advised that witnesses have the right under the rules of the House to be advised by counsel during their testimony. Dr. von Eschenbach or Ms. Glavin, do you wish to be represented by counsel today? Both witnesses indicate they did not. Therefore we will take the oath, and we will begin.

Dr. VON ESCHENBACH. Mr. Chairman, may I? Also at the table, joining me is Deborah Autor, our Director of the Office of Compliance, and would you swear her in as well, sir?

Mr. STUPAK. OK.

Dr. VON ESCHENBACH. Thank you.

Mr. STUPAK. Would you spell that for the record, please, just, Dr.——

Dr. VON ESCHENBACH. A-u-t-o-r.

Mr. STUPAK. A-u-t-o-r? OK. OK. Raise your hand, then.

[Witnesses sworn.]

Mr. STUPAK. Let the record reflect that all three witnesses have indicated the affirmative. That means they are under oath. Dr. von Eschenbach, you are the only one going to be giving an opening statement?

Dr. VON ESCHENBACH. Yes, sir, I will give the sole opening statement for this panel.

Mr. STUPAK. Welcome, and please, whenever you are ready.

TESTIMONY OF ANDREW C. VON ESCHENBACH, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; ACCOMPANIED BY MARGARET O'K. GLAVIN, ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES.

Dr. VON ESCHENBACH. Thank you, Mr. Chairman and members of the subcommittee, Mr. Whitfield. I very much appreciate the endurance and the attention that the panel and the committee has given to this very important issue. I very much appreciate the opportunity to engage in a dialog about FDA inspections of foreign pharmaceutical managers. But I think it is also apparent from everything we have heard this morning and this afternoon that we realize what the FDA has known for some time, and that is, this problem is much bigger than the number of FDA inspections that occur abroad. This is a problem that really addresses a much more global issue, and I want to begin by applauding the work of the committee and the committee's staff, particularly the counsel, who is present with us today. I want to appreciate the time that they have taken to update the FDA on the observations that they made during their recent foreign inspections, on which they accompanied FDA inspectors in China and in India. I find this dialogue to be very helpful to me and to the FDA staff.

We are well aware that, whether it is China or India, the fact of the matter, Mr. Chairman, is the world is and has radically and rapidly changed around us. We have heard about the enormous challenges but also the great opportunities that are now confronting us with regard to the issue of globalization. Mr. Whitfield was very kind this morning in commenting on his support of leadership at FDA to effect the kind of changes that we must effect if we are going to be responsive to these new challenges and these new opportunities. And it is not only with regard to leadership as it relates to identifying the need for and the application of resources through a budget process, but even more importantly our responsibility to present to you, to the administration, and most important to the American people a strategy and a plan as to how we would, in fact, begin to utilize these precious resources in the most effective way. And so I would like this afternoon to highlight just a few of the things that we are doing at the FDA to not simply build our capacity to better assure the safety of medical products or components that are produced abroad or that Americans use at home but also what we are doing to modernize the entire function and structure that is needed at the FDA if we are going to continue to be what we have just heard from our witness from Europe. We have been and are the world's gold standard, and we intend to continue to maintain that standard of excellence, but it will require change.

Mr. Chairman, we all know that, given the scale and scope of the problems that have been defined by you and other members of the committee, the solution to assuring the quality of imports does not reside only in increasing the number of inspections we perform abroad or even at our border. In fact, we agree, we must revamp our entire strategy, our entire game plan, and we are doing this as it relates to the importation of drugs and components of drugs from

other countries in exactly the same way that we are adapting our strategy and our approach to all other FDA-regulated products. We are adopting an entire life-cycle management and engagement process, from the very production, all the way through to consumption. And so much of our production now comes from outside our borders, we must be global in our regulatory approach.

This total life-cycle engagement is consistent with the first report of the President's Import Safety Working Group, on which FDA, along with other members of the Cabinet, is an integral part of the process. This import safety working group report emphasizes the key components of FDA's new strategy. We will be engaged in the total life cycle of these products through implementation of initiatives that address prevention, intervention, and our ability to respond. And we will do this in a way that first and foremost assures quality is built in to the products before they ever reach our borders, and we will use greater resources and more modern sources of science and technology to further enhance our efforts at both inspection and verification, as well as leverage those resources through collaboration and partnership with other government agencies, other governments abroad, other regulatory agencies, and, most importantly, the industry.

Let me give you one example of one of the tactics or implementations that we have incorporated in this approach, and that is our ability to use information technology, which is critical across the entire spectrum of prevention, intervention, and response. We recognize as the GAO pointed out that information technology infrastructure was a problem at FDA 10 years ago, and it is a problem today. But unlike 10 years ago, today we have technologies and capabilities that didn't exist in 1997. None of us is using the same model of computer or cell phone today that we did 10 years ago. We also have recognized the development in other spheres of data mining techniques and the ability to crosswalk through different data systems, and our opportunity to adapt these new technologies and these new strategies in IT is exactly how we will approach and are approaching the modernization of IT.

I would like to point out on the panel's charts that will be presented to you, if we could please put them up. The graphs are on your screen, and if we could put the charts up, that would be helpful.

[Slide]

Mr. Chairman, I would point out that this particular schematic is a very complex display of the various components of the information technology processes and components that are operative in our ability to oversee the diverse portfolio that FDA is responsible for regulating. As you can see on your left-hand side, the current state is, and as has been pointed out, there are multiple systems addressing multiple needs, but they have been developed independently for specific missions, and what has been absent is the ability to further integrate and coordinate those systems. We have been engaged in a very aggressive effort to migrate those systems into a unified, coherent, single FDA approach to IT technology.

Once we have accomplished that, on the right-hand side, all of those various applications will be able to have a degree of interoperability of information sharing and information analysis and

outcome assessment that literally has not been capable or able before, both because of technological limitations as well as, as we indicated, structural changes that needed to occur within FDA. In 2007, we brought in a Chief Operating Officer and a Chief Information Officer, both of whom had extraordinary experience in modernizing complex information technology infrastructures. We created the Bioinformatics Board at FDA to bring the operating components together to find opportunities for synergy and interoperability, and we are working with our external partners, particularly, for example, as it relates to inspections, our colleagues in the Department of Homeland Security-Customs and Border Protection, to further enhance our opportunities for interoperability and modernization of IT.

And we are allocating resources to this important issue. Our 2008 budget request, currently before Congress, includes $247 million for such efforts, and that actually accounts for 11 percent of the agency's budget, devoted and committed to modernizing and implementing the kind of information technology infrastructure that you and other members of the committee have been calling for.

In addition to just simply looking at the infrastructure, it is mostly and critically important to look at how we interact with, collaborate, and cooperate with our partners. This is a global problem, and it will require a global solution. Inspections will verify quality, but they don't create quality. Technology can exist, but it will never be able to replace the ability of people interacting with other people to create the kind of quality that Americans expect and will continue to depend upon.

And so FDA is taking a very aggressive approach in our effort to further enhance our own resources as it relates to our ability to expand our workforce with the great, qualified, talented people, as well as to collaborate more effectively with our partners abroad so that we can collectively address a problem that truly, as you heard from our colleague from Europe, is something that everyone in the world is concerned about.

Some of those opportunities are to expand FDA's international presence beyond its borders. We are committed to finding the kinds of options that you have discussed, namely, placing FDA staff on long-term assignments in key locations around the world, on a permanent basis. Our staff onsite in those locations would have a number of important advantages that weren't necessary in the past but are critical to the future. They will be able to, number one, work very closely, hand in hand, on an ongoing basis with our counterpart agencies, who must be important partners in this global effort. They will help build capacity in developing areas in which they have not had the fruits and the benefits of the kind of support that we have achieved or experienced here in the United States with regard to your support of the FDA. We will be able to provide technical assistance to foreign manufacturers to build quality in and improve products long before they come to us, and we will be able, as has also been indicated, on an ongoing basis to create opportunities for partnership that transcend cultural barriers, language barriers, and those things that separate us rather than unite us. And we will have the opportunity to leverage the impact of a

global industry expecting to produce and deliver global products around the world.

We will be able to continue to expand our government-to-government and agency-to-agency activities. Both Secretary Leavitt, myself, and many, many FDA staff have been engaged in substantial interactions with our counterparts, especially in China. I personally visited China and interacted with my counterparts, the Minister of Health, the head of the State Food and Drug Administration in China, and leadership of its export agency. We will continue these relationships to build and assure the kind of quality that is necessary and to be able to create the infrastructure that will assure that quality.

No one wants to live in the past, and neither you nor I, nor any member of the committee, is satisfied with the status quo of today. Together, I believe we can build for tomorrow the FDA that will continue to be the gold standard of protecting and promoting the health of not just Americans but everyone else in the world as well. I look forward to the opportunity to respond to any questions that you have.

[The prepared statement of Dr. von Eschenbach follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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STATEMENT OF
ANDREW C. von ESCHENBACH, M.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON OVERSIGHT AND

INVESTIGATIONS

U.S. HOUSE OF REPRESENTATIVES

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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs at the United States Food and Drug Administration (FDA or the Agency). I am pleased to be joined here today by my Agency colleagues, Ms. Margaret Glavin, Associate Commissioner for Regulatory Affairs, and Ms. Deborah Autor, Director, Center for Drug Evaluation and Research (CDER) Office of Compliance. Thank you for the opportunity to discuss the important issues relating to FDA's foreign drug inspection program.

FDA-regulated products include human and animal drugs, vaccines and other biological products, food and animal feed, cosmetics, and medical devices. FDA's regulation of these products is considered the "gold-standard" around the world and our goal is not only to maintain that standard but to continuously strive for improvement. Yet, in keeping this commitment to the American consumer, we do face significant challenges. We recognize that the world is evolving and our local markets now provide products largely from a global marketplace.

FDA is keenly aware that we must systematically assess these global market issues as they relate to drug products and other FDA-regulated products manufactured overseas. Therefore, we are developing comprehensive solutions to face these global challenges.

FDA REGULATION OF FOREIGN-MANUFACTURED DRUGS

FDA's monitoring of foreign-manufactured drugs is based on far more than foreign inspections. To comply with the Food, Drug, and Cosmetic (FD&C) Act, any entity that intends to import

drugs into the U.S. must ensure that the drug meets a number of quality and labeling requirements.

In the FD&C Act, Congress enacted provisions to create a relatively "closed" distribution system for imported drug products to help ensure the domestic supply is safe and effective by limiting the drugs and biologics that may be imported into the U.S. All "new drugs," which includes all finished prescription drug products, must be approved by FDA as safe and effective for their intended use. FDA approvals are manufacturer-specific and product-specific, and include many requirements related to the product, such as manufacturing location, formulation, source and specifications of active ingredients, manufacturing controls, the container/closure system, and labeling. Facilities that manufacture drugs for the U.S. market must meet FDA's current good manufacturing practice (cGMP) requirements.

When an FDA-regulated drug product is offered for import into the U.S., U.S. Customs and Border Protection (CBP) notifies FDA. If the product appears to violate the FD&C Act, FDA will give notice advising its owner or consignee of the violation and the right to provide testimony demonstrating why the article at issue is not violative or to request permission to recondition the product. If the product is ultimately refused admission, it must be destroyed unless exported by the owner or consignee within 90 days from the date of refusal.

FDA performs 100 percent screening of active pharmaceutical ingredients (API) and drug products entering into the U.S. to establish whether, if required, FDA has approved the drug product or the API is consigned to a plant that corresponds with its designated approval in the drug product application. Also, FDA screens whether the manufacturing plant is registered and

the drug is listed. FDA performs surveillance examinations of imported goods to check for compliance with U.S. requirements.

Another key tool is the Import Alert, which signals FDA field personnel to pay special attention to a particular product, manufacturer, shipper and/or importer. FDA issues Import Alerts for Detention Without Physical Exam (DWPE) when we have information that would cause future shipments of a product offered for entry to appear violative within the meaning of section 801 of the FD&C Act. This allows FDA field personnel to detain the product without physical examination, based on the appearance of a violation as documented in the Import Alert. Once FDA detains a product under 801(a) the burden shifts to the importer to demonstrate why, in fact, its product complies with U.S. law. In addition, FDA personnel also perform periodic filer evaluations to ensure import data provided to the Agency are accurate.

U.S. manufacturers also have a responsibility to ensure the safety of foreign-manufactured ingredients used for their finished dosages. U.S. manufacturers of finished dosage drugs that import APIs from abroad are to examine and test ingredients before using them in their drug products under cGMP. FDA may inspect a firm's foreign facilities and/or their domestic facilities to determine if the manufacturing facility meets the Agency's quality standards. In addition, FDA inspections routinely evaluate manufacturers' testing and controls of ingredients and supplies. FDA inspects all API manufacturers for compliance with cGMP prior to the approval of the dosage form's new drug application (NDA), abbreviated new drug application (ANDA), or biological license application (BLA). If during a domestic or foreign inspection, FDA determines that an imported API fails to meet specifications or is manufactured using unsafe practices, an import bulletin can be used to trigger testing of future shipments, or the drug can be subject to automatic detention at the U.S. border.

Foreign Inspections

FDA performs over 200 foreign drug manufacturing inspections per year. Exercising FDA's regulatory authority abroad can be challenging. In some countries, we need authorization from the relevant government to enter and inspect facilities and other countries have travel alerts that require FDA to take special precautions to ensure the safety of our investigators. Many of these firms are motivated to have FDA inspect their facilities because they have an application pending with the Agency that may require a pre-approval inspection.

Foreign inspections are more costly because of travel costs and special needs associated with travel in a foreign country. Foreign drug inspections are typically scheduled for five days. Depending on the product involved, we have scheduled inspections for as short a period as three days for a control testing laboratory, and up to two weeks for a sterile product.

There are approximately 800 FDA investigators trained to conduct foreign inspections in all program areas and 335 specifically for the drug program area. Also, CDER supports these inspections with additional technical experts and trained investigators. FDA typically solicits for volunteers from this specially trained cadre of investigators. The inspections are often conducted by one investigator who will conduct three, five-day inspections consecutively.

FDA foreign investigators are highly experienced and well-equipped. They often have many years of domestic experience and are dedicated to working long hours to accomplish an inspection in the allotted time. Some investigators speak foreign languages. FDA also relies on assistance from the firms' U.S. agents and representatives to translate if needed and help with logistical challenges that arise in traveling to a foreign firm. The investigators travel on official U.S. government passports requiring FDA to notify the U.S. Department of State and relevant

embassies. We are planning to strengthen our collaboration with embassy staff to assure our investigators are well prepared for local conditions.

Drug Ingredient Safety

Foreign activity in drug counterfeiting and contamination is an on-going concern for the U.S. and other nations. Ten years ago, counterfeit glycerin contaminated with diethylene glycol (DEG) killed nearly 100 children in Haiti. Last year in Panama, glycerin contaminated with DEG, traced to China, again caused scores of deaths. Recently, toothpaste imported from China was also found to contain DEG. To minimize the potential of DEG contamination of ingredients in the U.S., the Agency immediately issued guidance alerting drug manufacturers to perform testing for DEG contamination on all shipments of glycerin used in the formulation of drugs. FDA's CDER formed a task force, which developed a series of action items aimed at pro-actively addressing our susceptibility to similar pharmaceutical ingredient contamination and misbranding incidents.

As more pharmaceutical ingredients are sourced from abroad, an increased number of foreign intermediaries become involved in the supply chain. Discussions with the International Pharmaceutical Excipient Council (IPEC-Americas), a trade organization comprised of drug manufacturers and excipient manufacturers and distributors, has echoed our concerns and findings regarding the complexity of global supply chains and the lack of traceability of excipients to their original manufacturers. Pharmaceutical manufacturers can reduce the associated risks by obtaining intelligence about the distribution chains for each imported ingredient by establishing more robust systems and procedures to qualify suppliers of pharmaceutical ingredients and assure the identity and purity of batches of incoming ingredients.

IMPROVING THE OVERSIGHT OF FOREIGN MANUFACTURED DRUGS

Information Technology (IT) Enhancements

Since taking the position as FDA Commissioner, upgrading FDA's IT systems has been one of my top priorities. We expect these improvements will help address the challenges we face in the area of foreign inspections. Logistically, foreign firms are more difficult to track and more challenging to inspect than domestic firms. The data we have regarding foreign firms is not easy to confirm or check for accuracy because we cannot easily gain access to the firms. Foreign firms must register with FDA before shipping to the U.S. Because there is no cost to register, some firms register, but do not actually produce a product or ship products to the U.S, or discontinue shipping without any notice to FDA. The practice of registering without producing or shipping can create uncertainty at any given moment about the precise number of FDA registered firms from which to target inspections, often necessitating secondary data-source checking.

FDA does have the ability to capture the importation of drug products and the manufacturer of those products through its Operational and Administrative System for Import Support (OASIS) system. The information provided by the importer often leads to duplicate entries of manufacturers due to name, configuration, and address changes or does not accurately identify the site-specific manufacturer of the product.

We are working on more effective and efficient solutions to ensure the accuracy and validity of the data in our registration and import IT systems. FDA has set up the Bio-informatics Board (BiB) to address this issue for FDA. The Product Quality subgroup focuses on the issue of establishing accurate information on firms and their products. We are actively seeking other

means to identify duplicate entries, such as those caused by variations of the same name and address (e.g. use of third-party validation of non-confidential business information). Additionally, the Agency's current initiative to implement electronic registration of firms holds promise to redirect our resources from data entry, enabling us to focus instead on quality assurance of the data bases. In addition, the BiB directs the work and approves recommendations set forth by the Business Review Boards (BRBs). BRBs define business processes, driving outcomes enabled by IT services.

The Office of the Chief Information Officer is leading enterprise-wide IT transformation initiatives and establishing an aggressive two-year plan to rebuild FDA's critical IT infrastructure. Several key projects are underway that will sustain the transformation.

- FDA's Decision Support System will be enhanced to boost performance and expand the ability to rapidly access information critical to managing FDA's foreign drug inspection program. OASIS and Field Accomplishments and Compliance Tracking System (FACTS) will be migrated into 21st century database and hardware platforms to enhance critical functionality (target date: February 2008).

- FDA is implementing upgrades to the Agency's IT systems to increase efficiency of import entry review by allowing users to access multiple databases across the Agency under a single sign-on capability. Included systems are Drug Registration and Listing System (DRLS), Document Archiving, Reporting and Regulatory Tracking System, Mission Accomplishments and Regulatory Compliance Service (MARCS), OASIS and FACTS.

- FDA is developing and implementing a firm management and tracking system called Firm Management Services (FMS) that will allow users to input and search for firms in multiple repositories, improving the quality of data received by FDA and enabling the Agency to better screen imported products and identify firms shipping to the U.S. FMS will replace older, less effective technology used by FACTS/OASIS and older components of MARCS's applications.

- FDA is also developing a Firm Finder application to allow users to search firms in multiple repositories from one access point. Identifying and retrieving information about these firms is a key step in the evaluation of imports. Firm finder will use web services to integrate with legacy (FACTS/OASIS) and MARCS's applications.

- FDA is re-engineering MARCS, a major FDA IT program, to integrate and enhance several FDA systems, including OASIS and FACTS, by collecting and processing information obtained by or needed to support FDA field operations.

- FDA is working on FDA's Unified Registration and Listing System (FURLS) to integrate Center for Food Safety and Applied Nutrition, Center for Devices and Radiological Health, CDER, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, registration and listing systems.

- FDA has initiated software development of the Electronic Broker Information Center, a universal data interface application for filers, importers, or consignees to use a secure communication means to submit documents in support of entry review processes, location and availability data, view import entry and FDA line statuses, Notices of FDA Action, and perform firm and product data queries.

- FDA is working with CBP to ensure its planned Automated Commercial Environment (ACE) upgrade, a component of the International Trade Data System (ITDS), will provide real-time data feeds, ensuring that FDA receives all needed data elements electronically while harmonizing and validating information across centers.

- FDA is also engaging in ongoing cleanup of internal data to ensure rapid access to information in support of FDA import safety operations and upgrade of internal systems to synchronize and validate data across centers.

- FDA is developing and testing a system, which will utilize artificial intelligence in conjunction with analytical and inspectional data (foreign and domestic), and multiple data sources to identify products and shipments posing the greatest safety risks. The system is currently being evaluated for seafood products entering in the Port of Los Angeles and if successful will be expanded to other commodities.

- FDA is developing an Import Portal to allow Customs Brokers to more quickly exchange information with Import Reviewers about shipments/entries submitted for FDA review. The target for completion of development of this Import Portal is late FY 2009.

- FDA is making substantial improvements in its IT infrastructure critical to ensuring the exchange of data between its field offices and Headquarters, including CBP as it monitors products entering the U.S. FDA completed the network circuit upgrade in early 2007. The router, server, and Laboratory Storage Area Network (LABSAN) upgrade, installation, and operation lease agreement is in place and will be executed through October 2008. LABSAN is an infrastructure built to manage data and provide effective quality assurance to maintain data credibility and centralized data storage. LABSAN ultimately reduces time spent accessing and analyzing drug import data.

- FDA's Program Quality System is an Agency-wide initiative that encompasses an electronic mechanism for manufacturers' registration and product listings, as well as capturing inspection data from compliance reviews. FDA's Product Quality Business Review Board has completed the second phase of a three-phase project to harmonize the

processes for tracking regulated establishments and their products. Initial planning for this initiative should be completed by the end of December 2007.

International Efforts

FDA has a variety of cooperative relationships with foreign regulators, ranging from cooperation under a Free Trade Agreement, to agency-to-agency Memorandums of Understanding (MOUs), to informal arrangements established by exchanges of letters. A list of FDA's commitments appears on FDA's Office of International Programs, International Arrangements, web page (http://www.fda.gov/oia/default.htm).

FDA exchanges inspectional information with many foreign partners. Our relationships with some of these partners have become quite sophisticated and intense, developing to the point where we are communicating with them on a daily, and sometimes hourly, basis. FDA is currently engaged in the formal assessment of the efficacy of one foreign regulatory agency for more systematic use. Under the MOU between FDA and Swissmedic, the Swiss Agency for Therapeutic Products, technical experts have cooperated for three years on inspection collaboration with a desired endpoint of utilizing each other's inspection reports in making regulatory decisions. Both sides, however, would retain the authority to inspect manufacturers in the other country at any time.

FDA is also in the process of joining the Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S fosters cooperation among pharmaceutical inspection authorities in pharmaceutical good manufacturing practices (GMP), as well as developing and promoting harmonized GMP standards and guidance documents, training competent authorities (in particular inspectors), and assessing and re-assessing inspection authorities. FDA submitted a formal application to join PIC/S in September 2005. Upon acceptance, it will enable the

exchange of inspection reports and other inspection information with regulatory authorities. The PIC/S application process typically takes two years or more.

Another development on this front has been the establishment this year of the European Union (E.U.)-U.S. Bilateral Technical Working Group on Medicines Quality and Manufacturing. This group will have a major focus on utilizing shared resources through information exchange of inspectional data for plants in the U.S. and E.U. Another important planned activity of this group will be to share inspectional information from companies located in countries.

To promote and enhance the safety of all imported products, the President issued an Executive Order on July 18, 2007, that established the Interagency Working Group on Import Safety (Working Group). The Working Group, which includes representatives from 12 Federal departments and agencies, is tasked with reviewing the procedures, regulations, and practices for ensuring imported drugs, food, and other consumer products are safe. Secretary of Health and Human Services (HHS), Michael O. Leavitt, chairs the Working Group and FDA plays a key role. Secretary Leavitt and I traveled extensively throughout the country during the past few months visiting ports of entry and reviewing FDA field operations.

On September 10, 2007, the Working Group provided the President with an initial report on steps to improve import safety. The report, "Protecting American Consumers Every Step of the Way: A Strategic Framework for Continual Improvement in Import Safety," outlines an approach that can build upon existing efforts to improve the safety of imported products, while facilitating trade. It recommends that the Federal government work with the importing community in developing methods to address safety risks over the life cycle of imported

products and focus actions and resources to minimize the likelihood of unsafe products reaching our borders.

On October 1, 2007, the Working Group conducted a public meeting in Washington, D.C., to receive input from stakeholders. By mid-November of this year, an Action Plan based on the Strategic Framework will be provided to the President. The plan will reflect the public comments and recommend specific action steps the Federal government and stakeholders can take to enhance import safety at all levels.

Federal departments and agencies have already begun to implement high-priority recommendations from the interim report. By November 12, 2007, Federal entities that rely on IT systems in their review of imported cargo must develop implementation plans to achieve interoperability of their import data systems with ITDS managed by CBP. This requirement is consistent with the Security and Accountability for Every (SAFE) Port Act of 2006 and will ensure a single-window system for reporting on imports electronically.

The safety of products from China, as well as other trading partners, remains a concern for Secretary Leavitt and I, our staffers, Congress, and American consumers. The recent DEG episode has reinvigorated attention on China's regulation of its finished drug products, APIs, and excipients. We have limited knowledge of the quality of ingredients and products manufactured in China as this fast growing source is just beginning to put in place a national regulatory infrastructure. In the past four years, the number of FDA-registered drug manufacturers in China has at least doubled. The Chinese government is in the process of re-writing its existing cGMP for drugs. Drug manufacturers in China, and some other developing countries, comply with cGMP inconsistently and to varying degrees. Provincial authorities who conduct

inspections of drug manufacturing sites in China are not always equipped with the expertise needed for this complex undertaking.

The Office of Compliance within CDER conducted a series of educational workshops in China in December 2005 and April 2006 on current cGMP, in collaboration with the International Society for Pharmaceutical Engineering and Peking University. The workshops were intended to educate participants on current methods for compliance with cGMP, to ensure effective cGMP programs, and to further the common goals of FDA and providers of quality pharmaceutical products. The workshops were open to any professionals involved in the manufacture, control, and regulation of pharmaceutical products, including process/production engineers, manufacturing personnel, quality assurance/quality control and regulatory affairs professionals, consultants, regulatory investigators and cGMP compliance officials.

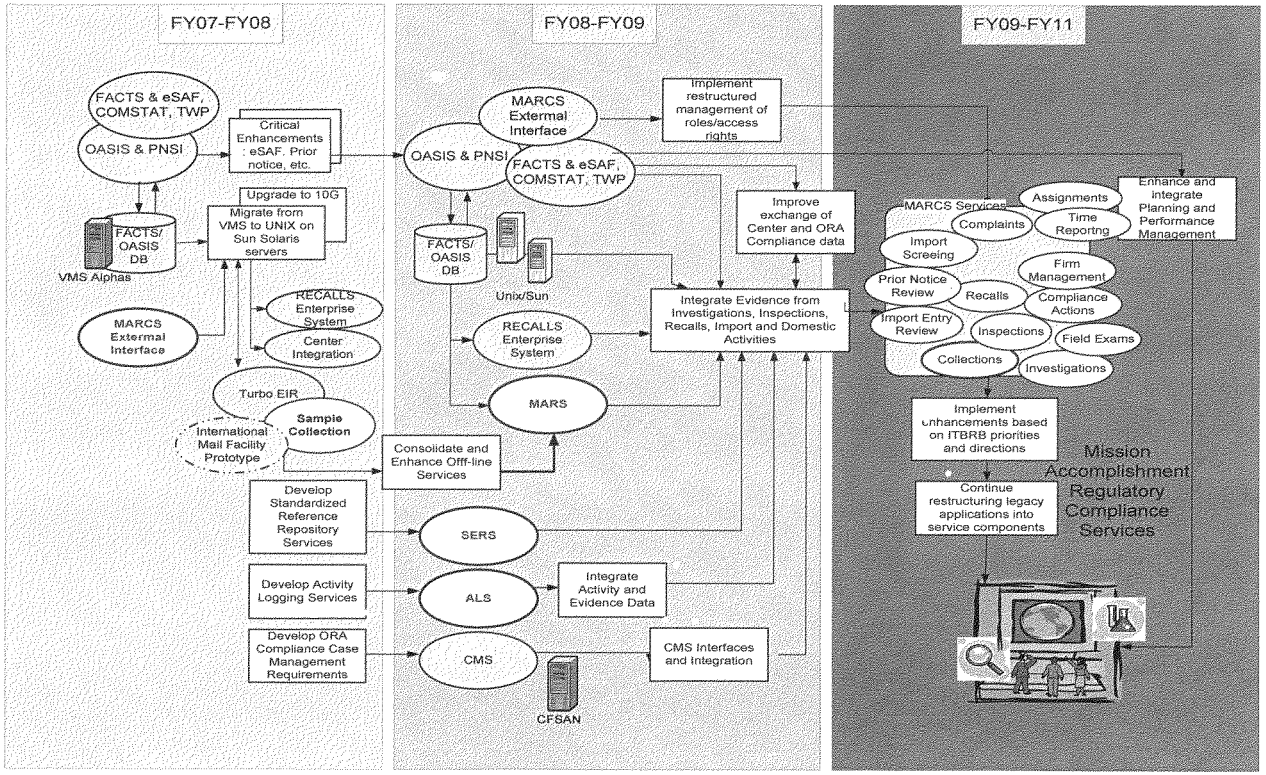
With the leadership of Secretary Leavitt, FDA and others within HHS are actively engaged with our Chinese counterparts in negotiating agreements that will include commitments relating to many FDA-regulated products to increase our confidence in the safety of these Chinese products that are exported to the U.S. A delegation of senior HHS and FDA officials are holding a second round of negotiations with senior Chinese officials in the Washington D.C. area. Represented agencies included the Chinese State Food and Drug Administration and the General Administration of Quality Supervision, Inspection and Quarantine. While these two agencies have very different roles, we are optimistic that we will negotiate an agreement with each agency that advances our nation's objectives, although perhaps with different approaches. We are continuing formal negotiations on two agreements, one on the safety of food and feed, and another on the safety of drugs and medical devices. I believe these talks are yielding significant

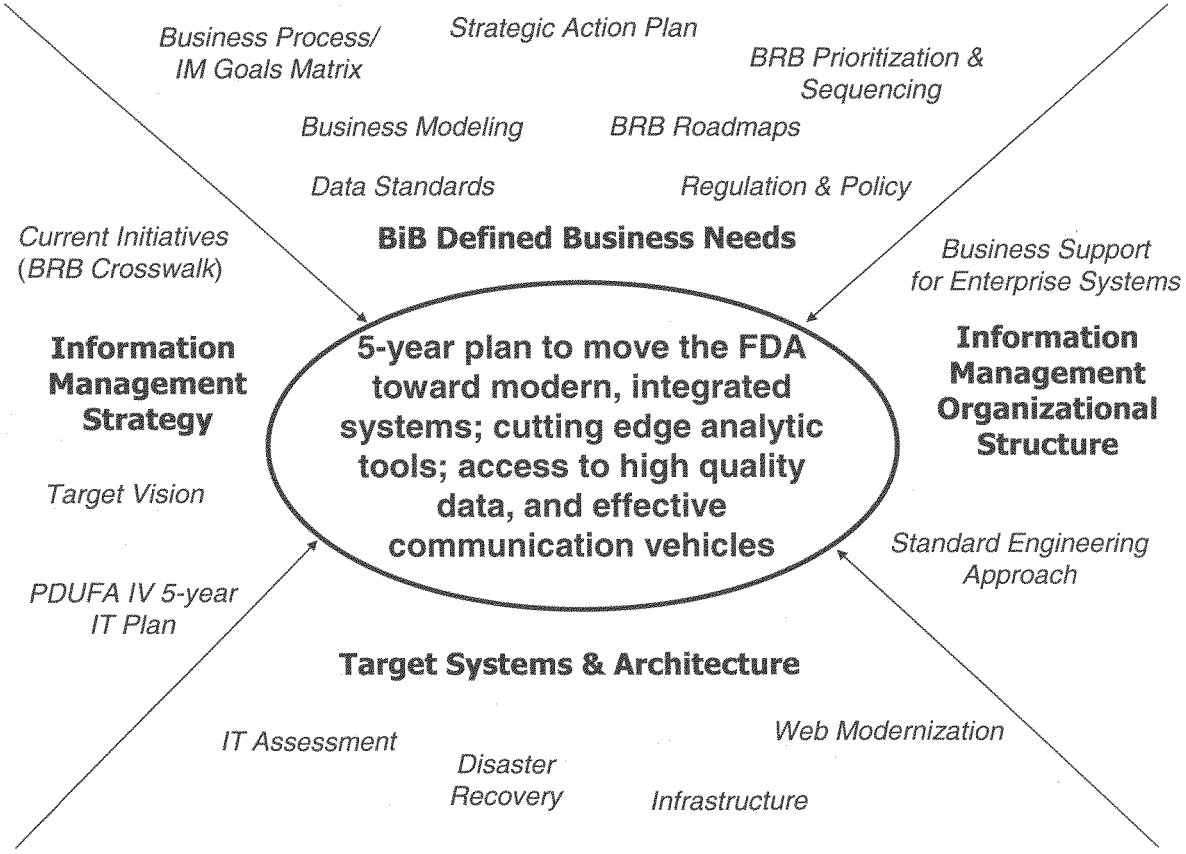
progress towards achieving two, strong, action-oriented documents, and I look forward to the signature of these documents.

CONCLUSION

Ensuring the safety of the drug products used by American consumers continues to be a top priority for FDA and we are working hard in collaboration with our Federal, state, local, and international drug regulatory partners. FDA is working diligently to efficiently and effectively use the resources and authorities provided by Congress to protect the public health of the U.S. and to help ensure that imported products are safe for American consumers. Despite the challenges which face us, the American drug supply continues to be among the safest in the world. Thank you for the opportunity to testify. I look forward to responding to any questions you may have.

Transition: From Legacy to MARCS




Business Process/
IM Goals Matrix
Strategic Action Plan
BRB Prioritization &
Sequencing
Business Modeling
BRB Roadmaps
Data Standards
Regulation & Policy
Current Initiatives
(BRB Crosswalk)
BiB Defined Business Needs
Business Support
for Enterprise Systems
Information
Management
Strategy
5-year plan to move the FDA toward modern, integrated systems; cutting edge analytic tools; access to high quality data, and effective communication vehicles
Information
Management
Organizational
Structure
Target Vision
Standard Engineering
Approach
PDUFA IV 5-year
IT Plan
Target Systems & Architecture
IT Assessment
Disaster
Recovery
Web Modernization
Infrastructure

Mr. STUPAK. Thank you, doctor, and thank you for being here today and for listening to the first two panels, their statements and their questions. The last time you were here at the end of the meeting, it was on food safety. You indicated at the meeting that it was important for you to hear the witnesses and what they have to say on issues affecting the FDA, and I appreciate that, and I appreciate your taking time to be here.

Dr. VON ESCHENBACH. Thank you, sir.

Mr. STUPAK. If I may, put up chart No. 3, the GAO chart. This was GAO's chart earlier today—right there——

[Slide]

Mr. STUPAK [continuing]. That they testified to and is part of their testimony. If you would take a look, the first country there listed is China, 714 plants with 13 inspections. How do we close that gap? And you can go right up the line to any country you want, but China and India are the biggest two exporters to the United States. How are we going to close this gap? I guess that is the whole question before this committee.

Dr. VON ESCHENBACH. Mr. Chairman, I think we have a number of strategies that must be and are being employed to close that gap. Number one, as I indicated in my oral testimony, we are engaged in government-to-government, minister-to-minister, regulatory-agency-to-regulatory-agency interactions to build capacity.

Mr. STUPAK. Right. We are glad to hear you say that, because when we met, committee staff met with Bill Steiger, he is your Director of Office of Global Health Affairs and Special Assistant to the Secretary of HHS, they told us basically they weren't interested. They just pushed back on every suggestion we have, like putting people in there, using other countries' inspectors to help us, so we are very glad to hear that. In fact, our staff on this committee, we are pleased to hear that. We think that is a good start. We think India is a country in particular that really wants the United States in there. The only question I would have, then, as you do these agreements, whether it is China, India, the UK, wherever, that country must have some kind of regulatory scheme, then, for drug safety and standards, much as ours, like——

Dr. VON ESCHENBACH. Yes.

Mr. STUPAK. Correct me if I am wrong, but China doesn't have any standards like that.

Dr. VON ESCHENBACH. Well, one of the important parts that you are pointing out, and I think it is an important part of this entire hearing's testimony, is that our presence in these foreign countries gives us the opportunity to build capacity. Build capacity, not just as it relates to our ability to inspect more effectively this growing portfolio of producers, but, even more importantly, to build capacity within those regulatory agencies.

Mr. STUPAK. Does that include putting people on the ground there permanently?

Dr. VON ESCHENBACH. Yes, sir. Yes, sir. As a matter of fact, we look forward to that as being a very key element——

Mr. STUPAK. We are glad to hear that, because we just think that is one of the ways to go. We are going to do five votes, and I don't want to keep you here with 45 minutes or waiting for us for an hour to vote, so let us try to buzz through some of these, if I may.

Earmarks chart that you had up there, in fact, the one that was up there before——

Dr. VON ESCHENBACH. Yes, sir.

[Slide]

Mr. STUPAK. The only caution I have on that is, we heard all that before in 1998 and the 2000 hearing. Because everybody was always worried about Y2K, and the FDA and all of them came in with these same things. They said, we will guarantee all these databases will talk to us. We are going to fix the Y2K problem, and these will all talk to each other. They will be integrated, and we won't have the problems. We still have the same problems today, so excuse me if I am a little skeptical, but why—my question, though, is, we heard from the previous panel that this PREDICT which is a program going on right now, you are using it for seafood, is doing all this, sort of getting interoperable, grabbing the key words from different databases, bringing it together. From what Mr. Nielsen said, who used to be in your Office of Regulatory Affairs, it is working, and it is working well. Why wouldn't you just expand that instead of create a whole new computer regimen that I am a little skeptical will work? If you have got one that is working now, why would you disregard that and go to a different system?

Dr. VON ESCHENBACH. We are not disregarding that, Mr. Chairman. As a matter of fact, PREDICT is one of the important models that we are beta testing, which I think has great promise because of the kind of data that it acquires and puts into our risk management system. In the interest of time, Mr. Chairman, I would like to submit for the record a much more detailed assessment of the specific steps that we are taking that I think will demonstrate to you that this isn't just same-old, same-old, or more planning, more ideas, but rather actual implementation of many of the things that you have been expecting and looking for. We heard this morning that there was a plan that was developed by some of the members of the first panel——

Mr. STUPAK. ISP, correct.

Dr. VON ESCHENBACH. And they seemed to indicate that nothing had been done. I had not had the opportunity to hear that before and respond to that, but I will be able to respond to you with regard to the fact of the matter is, many things have been done since that particular plan was put in place.

Mr. STUPAK. Is the ISP plan being implemented?

Dr. VON ESCHENBACH. Many parts and pieces of it are being implemented, and in fact many parts and pieces of that have been a core element of what is our more global import strategy that is a part of the presidential import quality initiative.

Mr. STUPAK. OK. You mentioned you are to spend——

Dr. VON ESCHENBACH. I will submit that for the record.

Mr. STUPAK. $247 million on this MARCS system to go to——

Dr. VON ESCHENBACH. IT, and I want——

Mr. STUPAK. Just in IT. Go to No. 4, if you would, chart No. 4, from GAO.

[Slide]

Mr. STUPAK. And here is what I want to know is, what resources is it going to take to implement your full plan, your IT plan, your

increased inspections? If you look at this chart right there, on the right-hand side of that chart as I am looking at it, that is 2007, that is the lowest line. The next one is 2008, where you predict a 40 percent increase in inspections. Where are you going to get the resources? Have you asked for additional resources for 2008? If so, how much is it going to take to get back to where we are actually doing inspections, which technically should be about 1,200 a year, not 300?

Dr. VON ESCHENBACH. We have asked and allocated in both the 2007 and have asked, and it is under consideration by Congress, in the 2008 budget, increases in our resources to be able to respond to this need, and we are continuing to build that business plan as we are in the process of preparing our 2009——

Mr. STUPAK. Will this be part of this presidential group you have looking at food safety and drug safety?

Dr. VON ESCHENBACH. Yes.

Mr. STUPAK. And they will put in a specific request for resources, then?

Dr. VON ESCHENBACH. We are building and have presented, and are in the process of building and presenting our 2009 budget request, and as I indicated we already had increases in the 2008 which hopefully when we move beyond the continuing resolution will have those resources to be able to be applied. What I also want to continuously emphasize, Mr. Chairman, is not only the absolute amount of resources, but, more importantly, how we are allocating them strategically, because I think we can leverage these resources to get more outcomes and just measures.

Mr. STUPAK. I agree. And I have to compliment the FDA today that while we are talking about foreign drugs and import into this country, you had a press release today saying the FDA raided a place today because the place they were producing the drug lacked FDA approval and remained under grossly unsanitary conditions by General Therapeutics Corporation of St. Louis, Missouri. So the problem isn't just other countries. It is even right here in our own country. And with that, let me turn it to Mr. Whitfield.

Mr. WHITFIELD. Thank you, and Dr. von Eschenbach, we are delighted you are here with us today. The first panel today, we had some distinguished panel with a lot of experience at FDA, and they talked about this internal import strategic plan that was developed at FDA, and that was about 3 years ago. From your understanding, why has this plan not been implemented as of today?

Dr. VON ESCHENBACH. Mr. Whitfield, I am going to ask Ms. Glavin to specifically comment on the number of initiatives that we have underway, as we speak, and have been underway at the FDA to do exactly that, to implement that plan. I regret that the people on the earlier panel commented that we are not aware of this, but I am pleased to present this to you.

Ms. GLAVIN. Well, we have already instituted a program to evaluate the accuracy of import filer information so that we can make sure that those filers are giving us accurate information. We have just posted on our contracting site a request for bids for verification of the registration data worldwide. This is to have an independent organization go out and actually see every one of these places so we have an accurate registration database. We are testing

the automated system that has already been talked about, the PREDICT system. We have developed a new——

Mr. WHITFIELD. Ma'am, what did you say about the PREDICT system?

Ms. GLAVIN. We are testing that. That is a system to automatically identify high-risk seafood imports for closer examination.

Mr. WHITFIELD. And you all have been operating that as a pilot program for, like, 3 years.

Ms. GLAVIN. No, no, no, sir. Just for a couple of months. We started this back in the summer. We have been developing it for about 3 years, but we have actually gotten it to the test phase at this point.

Mr. WHITFIELD. You have been developing it for 3 years.

Dr. VON ESCHENBACH. The software programs, and now they are being beta tested in——

Mr. WHITFIELD. But the information I had is that it had been operating as a pilot for 3 years, but you are saying it is—OK.

Ms. GLAVIN. That is right. It has just recently been put into a pilot phase. We have also developed a new screening test for use at ports of entries. It is a very important part of looking at imports. This gives more like rapid screening tests. We have a very interesting one that has just gone online. We are——

Mr. WHITFIELD. Well, let me just say that—I am sorry to interrupt you, but we have votes on the floor, and we have a very limited time, and—on this import strategic plan that was developed internally, and you were kind enough to go through it pretty precisely, are you saying that the majority of that plan will be implemented? Is that what you are saying?

Ms. GLAVIN. We are working on almost all of the recommendations in that plan and some of them have already come to fruition, but there is still many more that are in earlier stages. The ones I have mentioned are ones that are online.

Mr. WHITFIELD. And can you tell us as a part of the forthcoming President's Working Group on import safety whether you will be proposing a separate foreign inspection program?

Dr. VON ESCHENBACH. It will not be part of the import safety strategy per se——

Mr. WHITFIELD. Will not.

Dr. VON ESCHENBACH. But it is a part of FDA's strategy.

Mr. WHITFIELD. All right. Of the FDA's. OK. Now, you had also provided us with a graph of the IT program that you all are working on right now, which appeared to be pretty complicated——

Dr. VON ESCHENBACH. Yes, sir.

Mr. WHITFIELD. Which I am sure it is. Do you have any time table on that of when we——

Dr. VON ESCHENBACH. Yes, sir.

Mr. WHITFIELD. Could you——

Dr. VON ESCHENBACH. That is a 3- to 5-year implementation plan. It is mapped with milestones and outcomes. It has got a business plan underneath of it in terms of building our resources to support it, and it does require a cultural change, as was brought up earlier today, in terms of interoperability of cross-functional units, whether we call them stove pipes or silos, but that is all part of and integrated into the plan.

Mr. WHITFIELD. OK. But do you feel like when it is complete it should at least have the information necessary to assess the risk of foreign drug suppliers?

Dr. VON ESCHENBACH. We will have a plan that, number one, will get us better data in the first place, and that is critical. We must have quality data to start with and verification of the data. Two, better ability to acquire, integrate, and assemble that data, better opportunities to analyze and mine that data for information that we can then take regulatory action on.

Mr. WHITFIELD. Thank you, Mr. Chairman.

Mr. STUPAK. Well, thank you. I wish we had more time for questions, but I am afraid if we went and voted, we have five votes, that we would be there for an hour. So in lieu of keeping you for another hour, we will go vote. We will submit questions for the record and ask for your assurance that they will be answered in a timely manner.

Dr. VON ESCHENBACH. Yes, sir.

Mr. STUPAK. We would appreciate it. And thank you again for being , and thank you for sitting through this hearing.

Dr. VON ESCHENBACH. Thank you, sir.

Mr. STUPAK. That concludes all questioning. I want to thank all of our witnesses for coming today and for your testimony. I ask unanimous consent that the hearing record will remain open for 30 days for additional questions for the record. With no objection, the record will remain open.

I ask unanimous consent that the contents of our document binder be entered in the record, except for No. 9 and No. 11. We will scratch those two. So, without objection, those documents will be entered in the record.

That concludes our hearing. Without objection, this meeting of the subcommittee is adjourned. Thank you all.

[Whereupon, at 2:05 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

The New York Times
nytimes.com

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October 31, 2007

Chinese Chemicals Flow Unchecked Onto World Drug Market

By WALT BOGDANICH

This article was reported by Walt Bogdanich, Jake Hooker and Andrew W. Lehren and written by Mr. Bogdanich.

MILAN — In January, Honor International Pharmtech was accused of shipping counterfeit drugs into the United States. Even so, the Chinese chemical company — whose motto is "Thinking Much of Honor" — was openly marketing its products in October to thousands of buyers here at the world's biggest trade show for pharmaceutical ingredients.

Other Chinese chemical companies made the journey to the annual show as well, including one manufacturer recently accused by American authorities of supplying steroids to illegal underground labs and another whose representative was arrested at the 2006 trade show for patent violations. Also attending were two exporters owned by China's government that had sold poison mislabeled as a drug ingredient, which killed nearly 200 people and injured countless others in Haiti and in Panama.

Yet another chemical company, Orient Pacific International, reserved an exhibition booth in Milan, but its owner, Kevin Xu, could not attend. He was in a Houston jail on charges of selling counterfeit medicine for schizophrenia, prostate cancer, blood clots and Alzheimer's disease, among other maladies.

While these companies hardly represent all of the nearly 500 Chinese exhibitors, more than from any other country, they do point to a deeper problem: Pharmaceutical ingredients exported from China are often made by chemical companies that are neither certified nor inspected by Chinese drug regulators, The New York Times has found.

Because the chemical companies are not required to meet even minimal drug-manufacturing standards, there is little to stop them from exporting unapproved, adulterated or counterfeit ingredients. The substandard formulations made from those ingredients often end up in pharmacies in developing countries and for sale on the Internet, where more Americans are turning for cheap medicine.

In Milan, The Times identified at least 82 Chinese chemical companies that said they made and exported pharmaceutical ingredients — yet not one was certified by the State Food and Drug Administration in China, records show. Nonetheless, the companies were negotiating deals at the pharmaceutical show, where suppliers wooed customers with live music, wine and vibrating chairs.

One of them was the Wuxi Hexia Chemical Company. When The Times showed Yan Jiangying, a top Chinese drug regulator, a list of 186 products being advertised by the company, including active pharmaceutical ingredients and finished drugs, Ms. Yan said, "This is definitely against the law."

Yet in China, chemical manufacturers that sell drug ingredients fall into a regulatory hole. Pharmaceutical companies are regulated by the food and drug agency. Chemical companies that make products as varied as fertilizer and industrial solvents are overseen by other agencies. The problem arises when chemical companies cross over into drug ingredients. "We have never investigated a chemical company," said Ms. Yan, deputy director of policy and regulation at the State Food and Drug Administration. "We don't have jurisdiction."

China's health officials have known of this regulatory gap since at least the mid-1990s, when a chemical company sold a tainted ingredient that killed nearly 100 children in Haiti. But Chinese regulatory agencies have failed to cooperate to stop chemical companies from exporting drug products.

In 2006, at least 138 Panamanians died or were disabled after another Chinese chemical company sold the same poisonous ingredient, diethylene glycol, which was mixed into cold medicine.

China has an estimated 80,000 chemical companies, and the United States Food and Drug Administration does not know how many sell ingredients used in drugs consumed by Americans.

The Times examined thousands of companies selling products on major business-to-business Internet trading sites and found more than 1,300 chemical companies offering pharmaceutical ingredients. How many others sell drug ingredients but don't advertise this way on the Web is not known.

If the Milan show is any guide, most, if not all, are not certified by China's drug authorities.

China exports drug ingredients to customers in 150 countries, said Sun Dongliang, a Chinese trade official who helped organize his country's Milan exhibitors. Many suppliers have passed inspections by drug authorities and sell active pharmaceutical ingredients, or A.P.I.'s, of high quality, buyers say.

"Sometimes you can just have your lunch on the floor of the factory because it's so clean and so perfect, sometimes much better than in Europe," said Jean-François Quarre, a French drug company official who had a booth in Milan. But Mr. Quarre cautioned that he has seen the other side as well. "It's frightening."

At their worst, uncertified chemical companies contribute to China's notoriety as the world's biggest supplier of counterfeit drugs, which include unauthorized copies as well as substandard, even harmful, formulations. "Underregulated manufacturers are increasingly becoming the source of A.P.I.'s used in the production of counterfeit medicine," R. John Theriault, until recently Pfizer's head of global security, said in a statement to Congress.

Because United States drug regulators require pharmaceutical suppliers to meet high standards, the American supply chain is among the world's safest. But as China's chemical suppliers multiply, Congressional investigators are questioning the F.D.A.'s ability to protect consumers.

Even some Chinese chemical companies recognize their limitations in making pharmaceuticals.

"We don't have the resources and means to produce medicine," said Gu Jinfeng, a salesman for Changzhou Watson Fine Chemical. "The bar for producing chemicals is pretty low."

Even so, Watson Chemical advertises that it makes active pharmaceutical ingredients. But Mr. Gu said he would export them only to countries with lower standards than China, or if "we can earn really good profits."

A Trail of Steroids

Just days before the Milan trade show, United States officials made an announcement that brought home the global reach and attendant dangers of China's expanding chemical industry. The officials disclosed that they had dismantled a 27-state underground network for steroids and human growth hormone, arresting 124 people in "Operation Raw Deal."

The supply trail almost always led to China. Thirty-seven companies there supplied virtually all of the bulk chemicals, federal officials said.

Of the 37 suspect companies, all but one unnamed by the American authorities, The Times identified eight. Records show that six are uncertified chemical companies, including Hunan Steroid, which marketed its products at the Milan convention.

"Just want to see the old customers and develop the new market," said Sun Xueqin, a deputy export manager for Hunan Steroid. Ms. Sun said the company sold raw pharmaceutical ingredients in Europe and America and more advanced pharmaceutical ingredients in India, among other places.

Later, another Hunan official, Huang Zili, said the company did not sell to the United States, and declined to comment on the government's contention that Hunan was a supplier of bodybuilding drugs. Hunan has not been charged with any crime.

As serious as the accusations are in Operation Raw Deal, health experts say they believe that counterfeit drugs, particularly those sold on the Internet, pose a greater threat to a broader segment of the American public.

"The facts are irrefutable," Mr. Theriault, the former Pfizer official, told Congress. "The importation of counterfeit, infringing, misbranded and unapproved pharmaceutical products in the United States is increasing exponentially." Pfizer makes Viagra, one of the drugs most often counterfeited.

Finding uncertified companies feeding the market is not difficult. Orient Pacific International, the Milan registrant whose owner did not show up, advertised that it makes and exports pharmaceutical ingredients to "worldwide famous medical companies." The owner, Mr. Xu, is accused of selling counterfeit medicine to treat ailments like cancer, mental illness and heart disease, according to United States Immigration and Customs Enforcement, or I.C.E.

Mr. Xu shipped drugs to an Internet pharmacy, investigators say. But he also penetrated the highly regulated supply chain of legitimate distributors in Europe, said David A. Faulconer, a customs official. Acting on tips from large drug companies, federal officials devised a plan to stop him from doing the same in the United States.

Posing as a buyer, an investigator for the immigration and customs agency met Mr. Xu in Bangkok on March

6. Mr. Xu gave him "detailed suggestions for transshipment and smuggling techniques to evade United States Customs detection," federal records show.

After investigators bought multiple shipments of counterfeit drugs, Mr. Xu traveled to Houston "to consummate an agreement for widespread distribution of his counterfeit products in the United States," according to an affidavit filed in federal court. Federal agents arrested Mr. Xu, who has pleaded not guilty.

Another company exhibiting in Milan, Honor International Pharmtech, was also the subject of a customs investigation. In January, agents seized 3,041 fake Viagra pills sent by the company to a DHL shipping hub in Wilmington, Ohio, according to customs.

The shipment, disguised as grape seed extract, was destined for an Internet pharmacy in Central America, said agents who requested anonymity because the investigation continues.

"We do make grape seed extract," the company's managing director, Nie An, said in a telephone interview. He denied shipping counterfeit Viagra, but he acknowledged other indiscretions: making false advertising claims, using another company's import-export license and creating a fake corporate name.

"We don't really have a factory," Mr. Nie said, even though he advertised that he did. Honor International is just a trading company, he said, adding, "As a trading company, saying you can manufacture attracts business. It was fake advertising."

The Times found several other companies posing as manufacturers, thereby obscuring a drug's provenance. In a recent joint statement, chemical associations in the United States and Europe cautioned that globalization has led to a rise in complexity in supply chains, "increasing the potential for contamination, mislabeling or substitution."

Pharmaceutical ingredients can pass through three or four trading companies, none of which check their quality. The ultimate manufacturer may not realize the ingredients came from an uncertified chemical company.

Mr. Nie, for example, said he markets Viagra's main ingredient, sildenafil, through a partnership with a chemical company in a distant region that he has never visited. "We met them at a trade fair," he said. "This company didn't even have a booth at the fair. They were standing outside the entrance to the exhibition center, and they handed us a flier with a menu of their products."

He said he was trying to the reach the factory, which has no Web site, to fill a Croatian company's order.

"Our main markets are in Latin America — Brazil, Argentina, Uruguay," he said. "A little in Canada, a little in the United States. In Europe, we export to Germany, Russia, Italy."

But Mr. Nie faces an uncertain future. He said that Chinese investigators had recently visited his office, and that they knew about the seizure in Ohio.

Viagra is hardly the only drug that companies try to copy. The French drug maker Sanofi-Aventis grew weary of watching other companies sell knockoffs of its new diet drug, Acomplia, and alerted French authorities

that three Chinese companies were marketing their own version of the product at the 2006 pharmaceutical ingredient trade show, held in Paris. Six Chinese company officials were arrested.

One of those arrested in Paris was Jin Lijie, managing director of the Wuxi Hexia Chemical Company. Still, Wuxi Hexia showed up in Milan in 2007 selling a line of pharmaceutical ingredients.

Its representatives declined to be interviewed in Milan, or at its offices in the boomtown of Wuxi. "We are all young college graduates and we are still learning about the market," said an employee named Du Yanqun.

Factories on the Yangtze

A good place to find companies selling uncertified drug ingredients is Changzhou in the Yangtze delta, where the raw materials for chemical production are readily available and easily transported by canals and roads.

Several factories there sent representatives to Milan, including the Changzhou Kangrui Chemical Company. It makes pharmaceutical ingredients in an old converted steel plant. "I'm afraid it will leave you with a bad impression," said Zhou Ladi, a sales representative, as she gave a tour. She said Kangrui Chemical hopes to move into a new plant by early 2009.

"As long as we don't export products that are under patent in other countries, the government encourages us to export," she said.

To help find customers overseas, smaller factories enlist the services of people like Bian Jingya, export manager for a trading company called the Changzhou Wejia Chemical Company.

Ms. Bian said chemical companies are involved in all phases of drug manufacturing, including making finished products. Some, she said, "are under patent in other countries."

Ms. Bian, who was also in Milan, said the government should spell out more clearly what companies may and may not do. "If you want to be regulated, they will regulate you," she said. "If you don't want to be regulated, they don't."

The Chinese drug agency does not oversee the making of pharmaceutical raw materials, called intermediates, which are the building blocks for active pharmaceutical ingredients. "It is unrealistic for us to certify all factories that make intermediates and regulate them like medicine products," said Ms. Yan, the agency official. But if companies make active ingredients, a more refined product, then they must be regulated by drug authorities, she said.

When The Times pointed out that many uncertified chemical companies openly advertise active ingredients, Ms. Yan said that was illegal. "If there are in fact chemical companies that are making drugs without certification then this is very serious," she said. "These companies are not qualified to make medicine. They make chemicals."

Wang Siqing, managing director of the Changzhou Yabang Pharmaceutical Company, estimated that uncertified chemical companies make half the active pharmaceutical ingredients sold in China. "The stuff produced by chemical plants is clearly counterfeit medicine, but they aren't investigating," Mr. Wang said in

an interview at his office. "This has been happening in a regulatory void." He added that most chemical company exports go to unregulated markets in Africa or South America. "That's not to say these products don't enter the United States through these other countries," he said.

To find out how well American consumers are being protected from unsafe imported drugs, investigators from the House Energy and Commerce Committee recently accompanied F.D.A. officials on inspections of drug plants in China and India.

In a letter to the F.D.A. commissioner, the committee said that the agency was unable to provide such basic information as the number of firms exporting to the United States, and that overseas F.D.A. inspectors lacked necessary logistical support. A House hearing on F.D.A. oversight of foreign drug manufacturers is scheduled for Thursday.

"China alone has more than 700 firms making drug products for the U.S., yet the F.D.A. has resources to conduct only about 20 inspections a year in China," said Representative John D. Dingell, the Michigan Democrat who is the chairman of the House Energy and Commerce Committee. The F.D.A. said it would answer the committee's questions at the hearing.

Poisonings in Haiti

United States officials learned of problems with China's chemical companies in the mid-1990s while investigating the fatal poisonings in Haiti. Chinese authorities took no action against the uncertified chemical company that made the poison, diethylene glycol, or the giant state-owned trader, Sinochem International Chemicals, that exported it.

A decade later another state-owned trading company, CNSC Fortune Way, exported the diethylene glycol — also from an uncertified chemical company — that ended up in the deadly Panamanian cold medicine in 2006.

Chinese officials have known for years that uncertified chemical companies are producing active pharmaceutical ingredients. In 2004 the Chinese drug authority's newspaper cited complaints that some licensed companies "affiliate" with unlicensed ones to hide their illegal purchases, while others buy only a token amount from certified suppliers to pass inspection. "The impact of chemical products on the bulk pharmaceutical market hints at a much larger problem: a huge hole in drug safety," the drug agency publication stated.

Since the Panama poisonings, China is considering ways to corral the chemical industry. At Panama's request, Michael O. Leavitt, the secretary of health and human services, has pressed the Chinese government to step up regulation of chemical companies selling pharmaceutical ingredients.

American and Chinese health officials held their first high-level meeting in May, and hope to sign a memorandum of agreement in December. "The Chinese have finally come to the realization that their regulatory system needs repair," said William Steiger, director of international affairs for Mr. Leavitt's agency. But meaningful change will be difficult. Chinese authorities may not have enough investigators to weed out the many small chemical companies that are making drug ingredients.

And efforts to close the regulatory gap must overcome one particularly thorny issue: some uncertified companies accused of selling counterfeit drugs are owned by the government itself.

Ensuring the Safety of Imported Products

Q & A with Deborah Ralston

En Español | Chinese

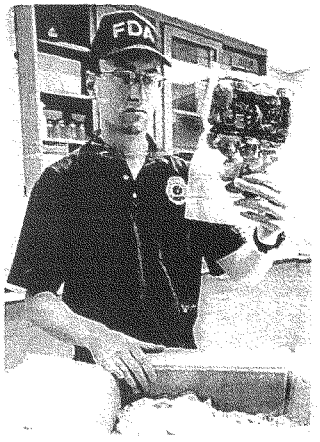
Printer-friendly PDF (331 KB)

As Director of FDA's Office of Regional Operations, Deborah Ralston coordinates the activities of a team of investigators and analysts located throughout the United States to ensure that regulated products destined for the U.S. market meet FDA's standards. Since joining FDA in 1972, Ms. Ralston has held various positions within the regulatory arena including investigator, compliance officer, and case review and enforcement officer.

Q. The number of imported goods that FDA regulates has more than doubled in the past five years. What is FDA doing to ensure the safety of these products?

A. FDA has a team of more than 2,000 dedicated, scientifically trained specialists who conduct inspections, collect and analyze product samples, do investigations, oversee recalls, take enforcement actions, and monitor the entry of regulated products at our nation's borders. We're responsible for overseeing the full range of FDA-regulated products: human food, animal feed, human drugs, vaccines and other biologics, medical devices, and veterinary drugs.

FDA analyzes about 30,000 import product samples annually. We also performed over 80,000 examinations of imported goods in the field and conducted over 800 foreign inspections during the past fiscal year—from Oct. 1, 2006, through Sept. 30, 2007.



Black Star / Michael Falco for FDA

An FDA imports specialist examining hardshell clams harvested in international waters. Laboratory analysis later confirmed the product to be safe.

Q. What is FDA doing to ensure that products from China are safe?

A. FDA has been in frequent discussions with Chinese officials. A delegation of senior Health and Human Services and FDA officials visited China in September, and FDA leadership went in October to begin negotiating agreements with our regulatory counterparts. These formal agreements will encourage a greater exchange of information and provide opportunities for us to collaborate with regulators and industry in China on the science and standards to ensure product quality and safety. This past year, we conducted approximately 30 inspections of manufacturing and processing sites in China for products that FDA regulates.

Q. FDA inspects or samples less than 1% of all FDA-regulated products seeking entry into the United States. Why doesn't the agency do more?

A. Because of the tremendous volume of imports—about $2 trillion worth of products each year from more than 150 countries—we cannot physically inspect or examine every product entering the United States. We use a targeted, risk-based approach, which means that we're working to inspect the right imports—those that may pose a significant public health threat.

For example, we work cooperatively with U.S. Customs and Border Protection to help identify shipments containing potentially dangerous foods and prevent them from entering the country. By law, certain information must be submitted to FDA about food products before they are allowed to enter the U.S. We keep our Prior

Notice Center open to receive this information 24 hours a day, 365 days a year. This means that FDA knows in advance when and where specific food shipments will enter the United States, what those shipments will contain, the countries and entities where they originate, and the facility where the food was manufactured.

So although we don't physically inspect every product, we electronically examine 100% of imported food products before they reach our borders. Based on criteria we have set up, an automated system alerts us to any concerns. Then we investigate further and, if warranted, do a physical examination of the product.

Q. How else is FDA improving its inspection capabilities?

A. We're providing our investigators with state-of-the-art inspection tools that can be used in the field to screen products and provide immediate scientific feedback so we can do inspections better. One tool that we'll soon be using is a device that can detect counterfeit drug products. It was developed by FDA's Forensic Chemistry Center and will be put to work by FDA investigators responsible for screening international mail.

Another new hand-held device that we're using can detect numerous elements in products, both food and drugs, many of which can be toxic.

We're continuing to explore existing technologies to adapt them for use in the field—not only for investigators, but also for use in our mobile laboratories. We collect samples of products in hundreds of locations, so it's not possible to have a laboratory established in close proximity to every collection site. We do have two mobile labs that can be sent to the borders when needed. Most recently, our microbiology mobile lab has been to the southern border to detect bacteria and other pathogens on leafy greens. And at the northern border, our chemistry mobile lab has looked for pesticides, poisons, and toxins on a variety of food commodities. No contaminated product was found during either deployment.

Q. What else is FDA doing to improve import safety?

A. We're working to shift responsibility to produce a safe product—and, in the case of a drug or device, an effective product as well—to the people who are presenting the product for entry into the United States. We want controls to be built in before products reach our borders. We are planning to increase our work with foreign governments and with our federal partners who may already have a presence in other countries to provide consultation to these governments on FDA standards and science. We want to help them develop their regulatory systems and be able to identify unsafe products so that those products never leave their countries. But if they do make it to our ports, our inspections at the border will provide a second layer of protection instead of a first layer, which is the case for many of them now.

We also have confidentiality arrangements with 31 foreign counterpart agencies in 17 countries that allow FDA to share and receive non-public information about imported products. For example, if the European Union has a problem with an imported commodity, they send us notices. We're able to input that data into our automated systems to learn whether or not we have received any of those products and to make sure that we set up the appropriate controls to ensure that those products don't come into the United States.

Q. What can consumers do to help protect themselves from potentially unsafe imported products?

A. Consumers need to maintain a level of awareness about their purchases. For example, people who order foreign drugs by mail, thinking they are saving money, can often get comparable generics here for less than what they're paying abroad. They're spending more money and the quality of the product is in question.

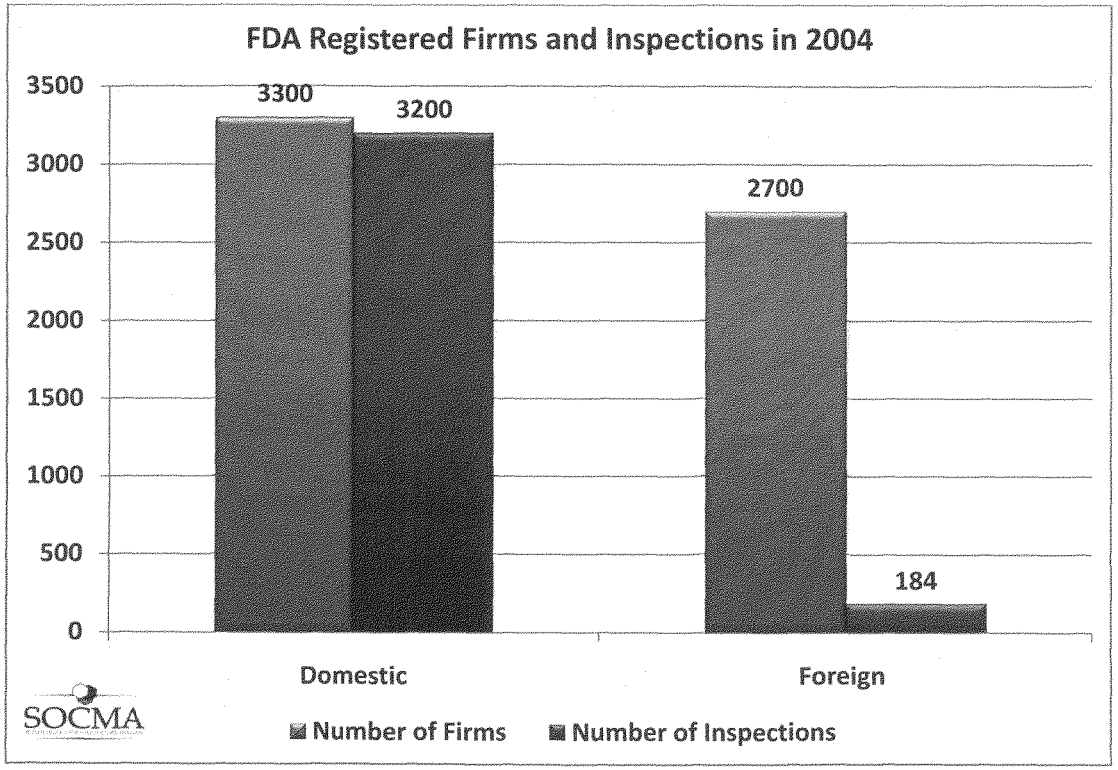
Pay attention to the media reports that come out from FDA, the U.S. Department of Agriculture, and other government agencies that regulate products for your protection to make sure you aren't using a product that has been recalled. Actively participate in reporting problems with products you purchase.

See "How to Report Problems With Products Regulated by FDA" at
http://www.fda.gov/opacom/backgrounders/problem.html

China Partnerships Page
http://www.fda.gov/oc/initiatives/advance/china.html

Date Posted: October 11, 2007

RSS feed for Consumer Updates [what is RSS?]



Number of firms data taken from the CDER 2005 Compliance Update presented by Kristen Evans at the 29th International cGMP Conference, University of Georgia, March 2005.

Number of inspections data taken from the 2004 CDER Report to the Nation published August 2005.

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

January 16, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

Thank you for appearing before the Subcommittee on Oversight and Investigations on Thursday, November 1, 2007, at the hearing entitled "FDA Foreign Drug Inspection Program: A System at Risk." We appreciate the time and effort you gave as a witness before the Subcommittee.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Subcommittee. In preparing your answers to these questions, please address your response to the Member who has submitted the questions and include the text of the Member's question along with your response.

In order to facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Wednesday, January 30, 2008**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Kyle Chapman, Legislative Clerk. An electronic version of your response should also be sent by e-mail to Mr. Kyle Chapman at **kyle.chapman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Kyle Chapman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Bart Stupak, Chairman
Subcommittee on Oversight and Investigations

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

MAY 23 2008

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the November 1, 2007, hearing entitled, "FDA Foreign Drug Inspection Program: A System at Risk," before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations. Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs, testified on behalf of the Agency. We are responding to the letter of January 16, 2008, you sent containing questions for the record. Subcommittee Chairman Bart Stupak's questions are restated below in bold, followed by FDA's responses.

1. **The databases of foreign drug manufacturers at the Food and Drug Administration (FDA) are poorly integrated, inconsistent, and difficult to access. Should FDA start from scratch and contact all foreign firms in its database, gather detailed information about their businesses, and enter this information into a new FDA database in order to include information on the following?**

   - **Manufacturing product**
   - **Last FDA inspection date**
   - **Next scheduled FDA inspection date**
   - **Products exported to the United States**

   Legacy information from old databases could then be integrated into the newly created one.

FDA agrees that its current databases related to foreign drug establishments and inspections need improvement, however, the Agency does not believe it is necessary to start from scratch and create a new database. FDA believes that the optimal strategy to achieve a goal of timely and accurate information includes:

(1) improvement and maintenance of a high-quality online registration process;
(2) access to third-party databases that can complement FDA's data verification and auditing procedures and reduce the need for manual verification; and
(3) improved integration of data and management of information across the various Agency databases.

FDA's proposed electronic drug registration and listing system (eDRLS) includes automatic reminders to firms that will be sent by e-mail. The eDRLS system would require firms to affirmatively renew their registration each year. We believe this would help eliminate some of the outdated registrations that occur in the foreign establishment inventory. Once finalized, the eDRLS database will provide a more accurate source of foreign drug establishment data in a more efficient manner.

FDA is not unique in seeking regular address verification and business identification for the industries it regulates. Address verification strategies must be planned to accommodate the fluid nature of corporate relationships and a rapidly changing drug manufacturing inventory. There are a number of commercial data and analysis firms that collect some of the information useful to FDA's registration and listing processes and some have had contracts with FDA. FDA is currently evaluating additional partnerships for address verification and analysis of the foreign inventory. For example, the Center for Drug Evaluation and Research's (CDER) Office of Compliance recently received data from a pilot study performed with a commercial business data firm in which corporate relationships and multi-component address verification were examined in the drug registration and listing system (DRLS) foreign registrations tables. The preliminary analyses show that commercial data sources can match the domestic companies' address and name fields with a reasonable degree of confidence for about 80 percent of the listings. In contrast, the matching at a similar degree of confidence in the foreign inventory is only about 54 percent. These results restate the complexity and challenge in maintaining an accurate and up-to-date foreign inventory. Most importantly, the third-party verification process can efficiently reduce the proportion of the inventory for which manual address and functional verification are needed. For example, high-quality databases need manual address verification for only about 10 percent of the database.

FDA is updating information technology (IT) resources to accomplish a goal of a single "status report" for its registrants. The status report is envisioned as accessing not only registrations and listings data (DRLS), but also a firm's inspectional status (e.g., from the Field Accomplishment and Compliance Tracking System (FACTS)) and importation activity (the Operation and Administrative System for Import Support (OASIS)). In order to achieve the challenging goal of unambiguous and information-rich status reports on registrants, we recognize the need for FDA's legacy databases to interact with each other. This is a major effort under FDA's Bioinformatics Board's (BiB) Product Quality and Compliance Review Board.

2. **Current law states that U.S. domestic drug firms must be inspected once every two years. Data made available at the hearing by the Government Accountability Office (GAO) suggest, however, that FDA has the resources to inspect foreign firms on average only once every 13 years. Is it fair that a U.S. domestic firm—operating in a highly regulated environment—is inspected almost every two years, and yet a foreign firm—which may be operating in a far less regulated environment—is inspected far less frequently?**

The Federal Food, Drug, and Cosmetic (FD&C) Act includes a statutory obligation to inspect domestic firms every two years and we strive to meet that requirement. Although we have incrementally increased the number of foreign inspections, we would like to conduct more. However, it should be noted that:

- As with FDA's domestic surveillance mandate, regulatory authorities in foreign countries have primary domestic responsibility to inspect products manufactured within their borders. We currently monitor the international industry by leveraging information from counterpart authorities, conducting increasing numbers of risk-based inspections, and performing inspections of sites as part of the pre-approval process.

- The Prescription Drug User Fee Act (PDUFA) program supports allocation of substantial resources toward pre-approval inspections of drug product and active pharmaceutical ingredient (API) manufacturing sites referenced in new drug applications so that the Agency may achieve its PDUFA review goals. The Agency must factor these PDUFA review goals for the selection and timing of a large percentage of its inspections overseas. Therefore, FDA inspects almost all domestic and foreign facilities cited in an application before a drug product is approved and shipped to the U.S. While FDA conducts fewer post-approval inspections of foreign facilities, FDA has stronger legal authority to exclude products from those foreign facilities from U.S. commerce (e.g., to refuse admission into commerce if they appear to be adulterated).

3. **Given the substantial difference between foreign and domestic inspection frequency, why has FDA not asked for more resources in order to close this gap?**

Drug inspections, including foreign drug inspections, are a priority for FDA. FDA developed its budget for drug inspections consistent with overall Administration budget priorities.

4. **Is the duration of time between foreign inspections—on average, every 13 years—deemed acceptable by FDA? If not, what is FDA doing to close this gap? Please provide specifics of this effort.**

FDA agrees that it can improve its foreign drug inspection program. The Agency performed increased current good manufacturing practice (cGMP) surveillance inspections in Fiscal Year (FY) 2007, but would like to conduct even more inspections. We have also taken the following specific steps since 2000 to improve the foreign drug inspection program:

- **April 1, 2000: Rapid Alert System,** a joint procedure for exchanging information, was implemented between the European Union (EU) and FDA to promptly alert authorities of quality defects, recalls, counterfeiting, and other quality problems that could necessitate additional actions or suspension from distribution of pharmaceutical/medical products.
- **October 2000: FDA Import Alert 66-66** was issued to alert districts to detain APIs offered for entry that are not manufactured by facilities listed in approved applications or are not being shipped to the approved finished product manufacturers.
- **September 2001: FDA adopted International Conference on Harmonization (ICH) Q7A, GMP Guidance for API Manufacturing,** which has been implemented by regulatory bodies worldwide setting quality and cGMP standards for API manufacturing.
- **2001: Establishment Evaluation System (EES) was expanded to several large import districts,** to enable identification of entries of APIs without approved applications.
- **February 2002: A foreign registration regulation** was implemented providing FDA with registration data on foreign firms and allowing the Agency to require foreign registration as a prerequisite for importation.
- **August 2002: Pharmaceutical Quality for the 21st Century Initiative – A Risk-Based Approach** is an ongoing initiative to encourage the early adoption of new technological advances by the pharmaceutical industry, to encourage implementation of risk-based approaches, to ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science, and to enhance the consistency and coordination of FDA's drug quality regulatory programs.
- **2003: Pharmaceutical Inspectorate (PI) program** was created providing a specialized team of experts in drug product manufacturing to conduct inspections of high risk firms. The PI is trained to conduct the more complicated and highly technical inspections. As of January 2008, 11 PI investigators have been credentialed.
- **2004: Establishment Evaluation System (EES) was further expanded.**
- **September 2005: Risk-based model for selection of manufacturing sites located abroad** was implemented for surveillance inspections to utilize our available resources more effectively and efficiently.
- **September 2005: FDA submitted its application to join the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S),** an international forum of regulators that fosters cooperation between pharmaceutical inspection authorities. When FDA is accepted, it may be able to exchange inspection reports or other inspection information with regulatory authorities. The PIC/S application process typically takes two years or more.
- **November 2005: FDA worked with ICH to finalize ICH Q8 (Pharmaceutical Development),** a guideline developed internationally that incorporates elements of risk and quality-by-design throughout the drug life cycle.
- **November 2005: FDA worked with ICH to finalize ICH Q9 (Quality Risk Management),** a guideline developed internationally that defines the principles of risk management that can enable more effective and consistent risk-based decisions by regulators and industry regarding quality.
- **2005-2006: FDA worked with Peking University, and the International Society for Pharmaceutical Engineering (ISPE)** to co-sponsor a training program for Chinese State Food and Drug Administration (SFDA) officials and industry representatives from

pharmaceutical, chemical, trade, consulting, and trade organizations to provide the latest updates from FDA on current regulations and guidance for pharmaceuticals, and interactive training workshops on solid oral dosage forms and API manufacturing. Since 2005, FDA has conducted four workshops in China related to cGMPs.

- **2006: FDA began to host the Forum for International Drug Regulatory Authorities** to provide information about the U.S. drug regulatory system in an organized and integrated manner to foreign regulators from throughout the world. The October 2007 forum included regulators from 14 different countries and the European Agency for the Evaluation of Medicinal Products (EMEA), including 11 individuals from China and 13 individuals from Taiwan.
- **July 2006: Peking University announced a new master's degree graduate program,** "International Pharmaceutical Engineering Management," the result of close collaboration between Peking University and FDA that was developed to accelerate the modernization of China's pharmaceutical industry.
- **August 2006: FDA issued its Quality Systems Guidance,** to encourage pharmaceutical manufacturers (both domestic and abroad) to implement a modern, comprehensive and robust quality system, consistent with cGMPs.
- **August 2006: FDA Proposed Rule on Electronic Drug Registration and Listing (e-DRLS),** if finalized, will create a system that enables FDA to keep manufacturers' registration and listing information current.
- **September 2006**: **FDA established its Bioinformatics Board (BiB)** to consolidate its IT infrastructure.
- **February 2007**: **FDA initiated a Pilot Electronic Registration Program,** which is expected to have electronic registration available publicly later this year.
- **May 2007: FDA issued guidance on "Testing of Glycerin for Diethylene Glycol [DEG]"** for pharmaceutical manufacturers, pharmacy compounders, repackers, and suppliers to prevent the use of glycerin that is contaminated with DEG.
- **May 2007: FDA convened a Drug Ingredient Safety Task Force** to develop a series of action items aimed at proactively addressing our susceptibility to similar pharmaceutical ingredient contamination and misbranding incidents.
- **December 2007: Department of Health and Human Services (HHS)/FDA signed a Memorandum of Agreement (MOA) with the SFDA of the People's Republic of China** to enhance the safety of drugs, excipients and medical devices exported to the U.S. from China. Specifically, the two countries are establishing a bilateral mechanism to help ensure these imported products meet standards for safety and effectiveness by building quality into the process from the start. SFDA will require firms that manufacture certain products intended for export to the U.S. to register with SFDA. SFDA will also work toward a system that will enable it to certify that firms that manufacture products, and the products themselves, meet HHS/FDA requirements.
- **2008: FDA is working to establish a foreign presence** in China to conduct audits and inspections, provide technical assistance, and exchange information on exported products.
- **2008:** FDA now has confidentiality arrangements with 19 agencies in 18 countries (including the EU) that permit FDA to share and obtain non-public inspectional information concerning foreign drug manufacturing firms. These relationships offer FDA substantial opportunities to leverage the inspectional resources of other countries'

competent regulators to obtain important information on the cGMP and other compliance status of foreign drug firms. Further, they provide for the exchange of timely information about products that have known or suspected safety problems.

5. Many experts have told the Committee that in order to ensure that foreign drug firms are meeting current regulatory standards, FDA should conduct inspections at least once every 2 to 3 years. Do you agree?

FDA believes that a risk based approach to using limited foreign inspection resources is most effective and pragmatic in terms of consumer protection. The two to three year inspection (or other means to reliably obtain compliance information) frequency that you propose generally could be appropriate for those facilities manufacturing high risk finished drugs or APIs, and products named in pending New Drug Applications (NDA) or Abbreviated New Drug Applications (ANDA). Some firms with questionable cGMP compliance histories may need more frequent inspections. Some API manufacturers and low-risk over-the-counter drug product manufacturers and testing laboratories can be inspected less frequently. Even among facilities manufacturing sterile drugs, the risk of non-sterility (one criterion for assigning a risk-based inspection frequency) will differ for aseptically processed drugs and terminally sterilized drugs. For some products, even the type of technology used can affect the level of risk.

Regular inspections of some foreign facilities by other reliable government authorities should also influence the frequency of FDA inspections. FDA also believes resources available for surveillance inspections should be heavily directed for facilities in countries not known to have robust regulatory systems.

6. Does FDA believe it can effectively understand the good manufacturing practice (GMP) status of a foreign drug firm if it is not conducting regular GMP inspections? If so, how?

The cGMP compliance status of any manufacturer, foreign or domestic, can change at any time. FDA can assess the cGMP compliance status at any given time by either an FDA inspection or by sharing inspection information from other reliable foreign regulators. Non-inspectional information such as consumer complaints, recalls, Field Alert Reports, reports from domestic firms, and Adverse Reaction Reports may also provide indirect information on non-compliance and can lead to scheduling a non-routine facility inspection.

7. What does FDA believe is the maximum amount of time that could occur between inspections that would ensure foreign firms are meeting U.S. regulations and standards?

We believe a risk-based approach is appropriate in determining when inspections of foreign firms take place. FDA does not believe there is one maximum amount of time between inspections of every type of facility. Most manufacturers cited in applications of prescription drug products who are routinely exporting to the U.S. should be inspected more frequently than other products that may present a lower risk. To maximize resources when we conduct a pre-approval inspection, we also conduct a surveillance inspection of the firm at the same time.

8. **China now appears to have the most facilities shipping drug products into the U.S., yet FDA dedicates only about 4 percent of its resources to inspections there. In fact, using current inspection rates and the number of Chinese firms likely shipping drug product to the U.S., it would appear that FDA can only inspect each Chinese firm on average once every 50 or so years. It is our understanding that FDA may soon consider placing FDA inspectors in China. Is that a correct understanding? If so, please provide a) how many inspectors will be based in China and in what capacity will they be functioning; b) the date (or schedule) this plan will begin to take effect, and c) the estimated projections this plan will have in closing the existing gap of FDA inspections of Chinese firms.**

FDA is currently pursuing the establishment of a presence in China. This presence would further facilitate FDA inspections in China, and other areas in Asia as necessary. Permanently placing Federal staff in a foreign country is an arduous task that involves a rigorous process, which includes not just the Agency and Department head, but several offices within the Department of State, the U.S. Ambassador in the specified country, and the host country government. In addition, such an endeavor must have the dedicated budget to support the function. If all of the above obstacles are addressed successfully, an FDA presence in China could become a reality in FY 2009. Recently, the Department of State approved the establishment of eight full time permanent FDA positions at U.S. diplomatic posts in the People's Republic of China, pending authorization from the Chinese government.

9. **The current largest recipient of FDA foreign inspection resources now appears to be India, where about 23 percent of FDA foreign inspections take place (according to GAO data presented at the hearing). Committee staff traveled to India to discuss with senior government officials the need for a permanent FDA office in India and China. In those discussions, both government and industry officials suggested that having an FDA office in India would be desirable and would foster better regulation of drug production for the U.S. market. Moreover, it would enable the U.S. catch up on needed inspections. Knowing India's interest in cooperating with the U.S. Government and its desire for more open inspections and safer drug manufacturing, is the Administration exploring with India a plan to open such an office? If so, please provide details on the approximate dates such an office would be set up, and the number of FDA officials that would be dedicated to it.**

Secretary Leavitt recently led a high-level delegation to India that included the Commissioner of Food and Drugs. Both HHS and FDA are committed to working with India on public health matters. The Secretary expressed to his Indian counterparts that we would be interested in engaging with them on exploring the possibility of establishing an FDA presence in India. At this point, a final decision has not yet been made whether to pursue this further.

10. **Many countries require FDA to conduct foreign inspections in languages other than English. In instances where an FDA inspection team requires a translator, one is provided by the company being investigated, most notably when Committee staff accompanied your investigators to China and India. However, Embassy personnel accompanying Committee staff remarked that the provided interpreter was not always providing an accurate translation. Since FDA examines numerous documents**

and witnesses manufacturing procedures, how often do you think inspection problems arise due to problems with translation? Why does FDA rely on the company being inspected to provide translation services? Why does the U.S. Government not provide FDA teams with a foreign language interpreter? Are there plans to address this matter? If so, how?

While some FDA investigators who do international inspections speak foreign languages, language ability is not a prerequisite for this work. This expertise is captured in an Agency-maintained database and when appropriate, we make efforts to select qualified investigators that may also speak the native language in the country being visited. It is correct that during the inspection process, FDA investigators routinely rely on assistance from firms' U.S. agents and representatives to assist with translating documents and oral conversations. However, we believe this practice has not affected our investigators' observations associated with the manufacturing process. Providing dedicated translators for each inspection would be costly. Having translators not cleared by the company or employed by FDA could present some confidentiality problems because FDA investigators review and discuss trade secret and other confidential information during inspections. This protected information could include whether a product receives approval, product formulations, and patented manufacturing processes and equipment. FDA understands the Committee's concern, however, and plans to further explore its options when determining the best ways to manage language barriers.

11. **Industry officials told this Committee that a domestic inspection can last several weeks, yet we understand that foreign inspections are often allocated only about three days in a schedule that typically contains three or four inspections spread over three to four weeks in various foreign locations. FDA inspectors interviewed by Committee staff have indicated there is not sufficient time to thoroughly inspect a facility in this timeframe. Given this reality, would a foreign FDA office help ease this timeframe constraint and lead to more through inspections?**

Because the majority of the cost associated with a foreign trip is often the travel costs, FDA attempts to schedule inspections in a manner that is the most resource- and cost-effective. FDA believes it is most cost-effective to schedule two to four inspections per trip, allowing for one firm to be inspected each week. In addition, depending on the inspection program area, the Agency can send more than one investigator to inspect a given site. We realize this time-commitment is a challenge for our investigators, and the Agency has introduced a number of incentives to help recruit volunteers for multi-week international trips.

Regarding the amount of time allotted for the completion of the inspections of each firm, we extrapolate the allotted time-frames from the actual amount of time it takes to conduct the same types of inspections domestically. If the need arises to extend a certain inspection because of problems or observations found, there is flexibility to allow more time for the inspection, and we would make arrangements for the inspection to be completed adequately. We rarely need to extend international trips beyond pre-determined inspection times.

In addition, as mentioned in response to question eight, FDA is pursuing establishing a presence in China. This presence would further facilitate FDA inspections in China, and other areas in Asia as necessary.

12. How do inspection plans differ when condensing a several week long inspection of a domestic firm, to a three-day inspection of a foreign firm? In what ways do foreign firms receive less scrutiny, compared to the more thorough inspections of domestic firms? Please provide specific details.

We believe that the quality of foreign drug inspections is similar to that of domestic inspections. A foreign drug inspection trip is typically scheduled for three weeks and includes three drug facilities. Each inspection typically takes about one week. Depending on the product involved, we have scheduled inspections for as little as two to three days for a control testing laboratory, and up to two weeks for a sterile product.

The scheduling process for foreign inspections, and the time dedicated to conduct an overseas inspection, takes into account the domestic historical average time for a particular type of inspection. Accordingly, inspections are planned in advance and the scheduled time to complete the inspection reflects the length of time it historically takes to conduct a domestic inspection. In addition, since these inspection schedules are arranged in advance and are difficult to change, foreign inspections are reserved for the Agency's more senior investigators.

13. It is our understanding that the foreign inspection program is a voluntary program for FDA inspectors. Additionally, many foreign inspection trips can be arduous and may require difficult travel to remote regions of the world, sometimes placing FDA inspectors' health and safety at risk. FDA has had difficulty in getting volunteers to conduct inspections for some parts of the world. What happens when you are unable to find a volunteer for a required foreign inspection? Has the agency ever been unable to recruit volunteer inspectors, thus requiring it to direct an employee to conduct a foreign inspection?

FDA would direct investigators to conduct foreign inspections when/if qualified volunteers could not be identified, and has done so on a few rare occasions.

14. Is there any current effort to retool the foreign inspection program to either provide more incentives to go on foreign inspections or to create a permanent foreign inspection workforce whose entire mission is solely to conduct inspections abroad?

The Agency currently has a number of incentives that are designed to increase the number of volunteers that would be willing to conduct foreign inspections for trips lasting three weeks or longer. These incentives are reflected in the enclosed Memorandum of Understanding between FDA and the National Treasury Employees Union (NTEU). In addition, we are currently reviewing this program and attempting to identify additional incentives and approaches to enhance our ability to schedule and perform foreign inspections.

15. FDA inspectors receive specific training to specialize in a particular inspection area, such as drugs, medical devices, or even the inspection of biomedical research trials. Has FDA ever directed an employee to conduct an inspection outside their area of expertise?

No. Investigators are nominated to the foreign inspection cadre consistent with the procedures referenced in Field Management Directive 13 and 13A, which directs that investigators meet specific criteria. It should also be noted that investigators may have multiple disciplines that would allow them to conduct inspections in multiple program areas.

Generally, investigators in the international inspection cadre meet the following basic requirements:

- Grade GS-12 (Journeyman Level) or above;
- Completed 6-months of on-the-job training using the FDA *Investigational Training Manual*;
- Completed Basic Law and Evidence Development course;
- Completed Investigative Interviewing course;
- At least three years experience conducting independent inspections in preferred program area(s);
- Demonstrated ability to prepare concise, accurate, and timely Establishment Inspection Reports (EIRs) and FDA 483 reports, pursuant to appropriate guidance;
- Demonstrated ability to communicate orally; and
- Excellent working knowledge of FDA's laws, policies, and procedures. As a representative of FDA and the U.S. Government, the candidate must have a demonstrated professional demeanor and ability to communicate Agency requirements, policies, and procedures.

In addition, investigators generally meet the following specific requirements:

Drug Investigators: Successfully completed Basic Drug Manufacturing Quality Control course and Industrial Sterilization (or equivalent);
Device Investigators: Successfully completed Basic Medical Device Training course and Process Validation or Industrial Sterilization (or equivalent);
Biologics Investigators: Blood Banks/Plasma Center: Successfully completed Basic Blood Banking and Plasmapheresis course and Advanced Blood Banking and Plasmapheresis course (or equivalent). Biologics Products: Successfully completed Drug Manufacturing and Quality Control and Industrial Sterilization course (or equivalent);
Food Investigators: Successfully completed Low-Acid Canned Food (LACF) or Seafood Hazard Analysis and Critical Control Points (HACCP) and Basic Microbiological Training course; and
BIMO Investigators: Successfully completed Clinical and/or Non-Clinical Bioresearch Monitoring Training course (or equivalent).

In preparing for an inspection, qualified investigators typically review the assignment, the appropriate compliance program, the firm history, as well as any specific guidance for industry that could be relevant to the type of firm being visited.

16. We understand that foreign firms—due to visa requirements and other factors-are often given several weeks notice of an impending inspection, whereas FDA can make unannounced inspections of a domestic firm. Does this factor grant an unfair advantage to foreign firms, because it allows them to "prepare" for an inspection well before FDA inspectors arrive?

While the Agency can theoretically perform an unannounced foreign inspection in most countries, it should be noted that some countries require clearance from the local government through the visa process to enter. Recently, some FDA staff proposed performing unannounced inspections in certain circumstances to further support the Agency's efforts to ensure the quality of imported drug products. The Agency intends to pursue the feasibility of unannounced foreign inspections and will evaluate whether such inspections are practical on a case-by-case basis. One challenge to this approach is ensuring that the appropriate personnel and records are present, as well as making sure that the firm to be inspected will be manufacturing during the time of the inspection.

There is no requirement in the FD&C Act to provide advance notice of inspections to foreign facilities, but there may be a practical need to do so. For example, a translator may be necessary for the inspection or there may be security concerns. It is also possible that a foreign firm could deny FDA access to their facilities. In some countries, the foreign government requires FDA to notify it of inspections to be performed and the foreign government may provide advance notice to the firm. In addition, international agreements may exist, which determine or limit the actions the Agency is able to take in the foreign country. Lastly, a foreign country may issue a visa to FDA staff based on information about the purpose of the visit provided at the time of application.

Thank you again for the opportunity to testify. Please let us know if you have any further questions or concerns.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosure

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Bart Stupak, Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce

MEMORANDUM OF UNDERSTANDING (MOU)
BETWEEN
THE FOOD AND DRUG ADMINISTRATION (FDA)
AND
THE NATIONAL TREASURY EMPLOYEES UNION (NTEU)
REGARDING
MANDATORY FOREIGN INSPECTION ASSIGNMENTS

FDA and NTEU agree that they are committed to treating domestic and foreign inspection assignments equally and that foreign inspections are part of the overall Agency work plan. Accordingly, the Parties agree to the following:

1) The FDA will rotate inspections fairly and equitably among similarly qualified employees.

2) In order to encourage volunteers for foreign inspections, the FDA will announce a call for volunteers on a semi-annual basis to participate on international inspections. This national volunteer list will identify traveler, area of expertise, and country and time preferences for travel. This list will be the first consideration for identifying employees to conduct foreign inspections.

   If management does not select a volunteer for an inspection from the national survey, inspection assignments will be issued on a regional basis at which time the region will work to identify a qualified volunteer by disclosing the assignment request to all qualified employees within the region.

   If no volunteers who apply for the inspections are selected or if no volunteers apply, then FDA will make every reasonable effort to assign the inspections on the regional/district level using the following assignment process:

   a) To any qualified GS-13 employee;
   b) To any qualified GS-12 employee;
   c) To any another qualified employee.

   All assignments listed above will be made on the basis of regional inverse seniority based upon HHS Entry On Duty date (EOD). Once an employee is chosen for (and performs) the inspection, the employee's name then goes to the bottom of the inverse seniority list based on grade.

In the event that the Agency adopts a PD containing a specific percentage of time to be spent in the international arena, qualified employees on this PD will be considered by management prior to a), above.

3) From October 1, 2003 to September 30, 2004, qualified employees GS-12 or below will not be assigned to perform a foreign inspection trip more than once per year.

4) All volunteers and assigned employees may switch their scheduled foreign inspection assignment with an appropriately qualified counterpart within their region, contingent upon management approval.

5) Hardship Exemptions: If an employee who is assigned to perform a foreign inspection is unable to accomplish the work assignment due to an emergency or unforeseen circumstance, they should notify both District management and DFI immediately. Employees may be excused from foreign inspection assignments by management upon a showing that they have valid extenuating circumstances present that would not allow them to perform the assignment. Valid extenuating circumstances are, primarily, conditions outside the control of the employee which would preclude them from being able to travel abroad without some economic or personal harm otherwise occurring. The request for an exemption should be made in writing within five (5) workdays of receipt of the foreign inspection assignment. The circumstances surrounding an employees inability to conduct the foreign inspection will be reviewed on a case-by-case basis and management will make the final decision on the employee's work assignment. Any management denials of such requests will be provided in writing to the employee within five (5) workdays of the request. All denials are grievable through the negotiated grievance procedure.

6) From October 1, 2003 to September 30, 2004, for qualified employees GS-12 or below who did not volunteer for the inspection assignment, foreign inspections will normally be limited to a period of no more than two weeks.

7) Employees will always be provided with contact information for an alternate or back-up trip coordinator to handle any necessary travel or inspection changes when the primary coordinator cannot be reached. However, in the absence of access to a travel planner, employees may make their own travel arrangements.

8) Employees that are required to take numerous short legs of a trip once they have arrived in the country where the foreign inspection is to occur may advise the travel planner as to their preferred mode of transportation for those legs of the trip.

9) The FDA will provide non-volunteers assigned to conduct foreign inspections as much advance notice as possible, but normally no less than eight (8) weeks prior to the assignment.

The FDA will normally provide non-volunteers assigned to conduct foreign inspections with advance notice of ten (10) calendar days of their full travel schedule, including information regarding any dangerous conditions in-country as defined by the State Department.

All affected employees will be given the opportunity to attend the FDA/ORA International Inspections Course, preferably prior to performing their first foreign inspection.

The FDA will provide all employees that perform foreign inspections with travel services, medical insurance coverage, and/or emergency transportation/evacuation insurance coverage.

13) The FDA will authorize business class travel in accordance with 41 CFR 301-10.124(i) of the Federal Travel Regulations, and other applicable laws and regulations.

14) Up to fifteen (15) hours of overtime or compensatory time per week will be authorized in advance for workdays in excess of eight hours for all trips involving transoceanic travel. For all other trips (e.g., Canada and Mexico) employees will be authorized up to ten (10) hours per week for workdays in excess of eight (8) hours. All overtime must be requested and approved in advance.

15) Employees will be expected to complete the write-up of reports normally not later than thirty (30) calendar days after they return from conducting the foreign inspection.

16) In order to guarantee the safety of FDA employees and consistent with existing FDA policy, two (2) employees will normally be assigned as a team on any foreign inspection trips to countries given travel advisories or warnings by the State Department and other countries as determined by management. The team will include at least one (1) employee who has prior experience in foreign inspections.

Translators will be provided for employees while performing inspections abroad whenever there is no designated English-speaking company representative available at the firm being inspected.

18) As a resource, the FDA will provide, upon request, the name(s) and contact information of employee(s) who have conducted foreign inspection(s) in a particular country of interest.

19) Cell phones that connect internationally will be provided to all employee teams performing a foreign inspection for the duration of their time abroad. In the event that

a cell phone is unavailable that is compatible with the country in which the foreign inspection is being performed, an international calling card will be provided to the inspection team.

20) The FDA will request that the firms being inspected in countries given travel advisories or warnings by the State Department and other countries as determined by management, provide a driver and/or a company contact for employee(s) assigned to inspect the firm. Management will continue to make reasonable efforts to ensure that strict security practices are adopted for all employees in these types of countries, including providing a contact that may be reached at all times in case of emergencies.

In accordance with government rule and regulation, employees will be allowed to process ATM transactions on their expense vouchers in order for them to avoid carrying massive amounts of traveler checks or cash at any one time. This authorization will be stated on all foreign travel orders.

22) DFI does not routinely schedule inspections in countries that have an associated State Department warning. The State Department warning is used as a signal that such requests for inspection need to be further evaluated on a case-by-case basis. During this assessment, FDA weighs concerns about the safety of its investigators against the public health benefits to US citizens of having access to the product being inspected. For routine inspections, FDA has historically made decisions on the side of caution for the safety of its investigators. For products that are innovative breakthrough products or are considered medically necessary, FDA generally errs on the side of public health benefit and requests volunteers to conduct the inspections. FDA has applied this policy uniformly to avoid establishing precedents for one country that could not be consistently fulfilled in other countries for which we have similar concerns about travel. The Agency will normally only use volunteers to conduct inspections in countries that have an associated State Department warning.

23) A lack of experience with foreign inspections will be considered when the performance of any employee on such inspections is evaluated.

24) Management will hold formal 7114 meetings with all affected FDA employees regarding the changes to the foreign inspection program and this MOU. A representative from each appropriate NTEU chapter will be notified in advance of the meetings and afforded the opportunity to attend.

25) This MOU will become effective upon the signature by both parties. The MOU will expire upon the expiration of the current FDA/NTEU collective bargaining agreement (CBA), or on the effective date of its successor, whichever occurs first. The Parties recognize that this MOU will remain in effect during the interim between the expiration of the current CBA and the effective date of any successor agreement.

For the FDA:

Diana Kolaitis
RFDD, Northeast Region
Chief Negotiator

Execution Date: June 11, 2003

For the NTEU:

Daniel P. DiJames
National Negotiator

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

cc: N. Rogers
R. Hackett

Date September 29, 2003

From John M. Taylor, III
Associate Commissioner for Regulatory Affairs

Subject Voluntary Foreign Inspection Program Improvement - FDA/NTEU MOU

To Barbara Sheehy
National Rep - NTEU Signed 10/16/03

Enclosed is the outline of my review and consideration of the recommendations submitted to my attention by the joint FDA (ORA)/NTEU Voluntary Foreign Inspection workgroup (VFI). In addition, I would like to acknowledge my appreciation of the collaborative effort of the workgroup in their deliberations under what can be considered a difficult situation given the logistical factors encountered in bringing the group together. As reference, my charge to the workgroup (as required under our current MOU) was as follows:

To develop options (incentives) for consideration that would:

- Improve the voluntary foreign inspection program;
- Increase participation in the program by a greater number of employees;
- Encourage and promote the program as a viable mechanism to accomplish the Agency's foreign inspection commitments; and
- Expand training options that support the program

After careful consideration and consultation with ORA senior managers, my decision regarding each recommendation is outlined in the chart below.

Voluntary Foreign Inspection Workgroup Recommendations	ACRA's Decision
#1. Employees will be given a total of $300 of incentive pay for each standard foreign inspection trip. If during the course of the standard trip assignments are cancelled that result in a reduction in inspection time due to circumstances out of the employee's control while they are in travel status, the employee will receive the $300 award. *Note: Work products must be fit for use in accordance with IOM requirements. Incentive awards will be issued twice per year (mid year and end of year).* *Note: NTEU and FDA will need to sign an MOU agreeing that this pay will not be a part of the CBA Awards Program.*	Approved, ORM to coordinate with ORO/DFI Accepted - For the purposes of this memorandum and agreement the standard foreign inspection trip is considered to be 3 weeks in length.

#2. Employees will be given the option to use a total of six hours per trip of FWAP to be used before the foreign inspection trip in order to prepare for the trip. (e.g. used for such things as money exchange.)	Approved
#3. Solicitation of volunteers for the foreign inspection program will go to all employees. The employee responses to the survey will go to the District coordination point. Management will decide if employees are qualified and subsequently prepare a consolidated list of volunteers to DFI. The district will make the volunteer list available to employees within the district. DFI will consolidate the district responses and prepare a National list of volunteers. The national volunteer list will be the first consideration for identifying individuals for foreign inspections. DFI will make a name request to the employee's home district management. If a requested person is subsequently not available, and if another volunteer in that district can not be identified, the district initially contacted will refer to the national volunteer list as they work to identify a traveler within that region. The region will have the option to look for volunteers within their region or from the national list. *Note: Any employee under a PIP or administrative action will not be qualified for the National volunteer list.*	Approved Accepted

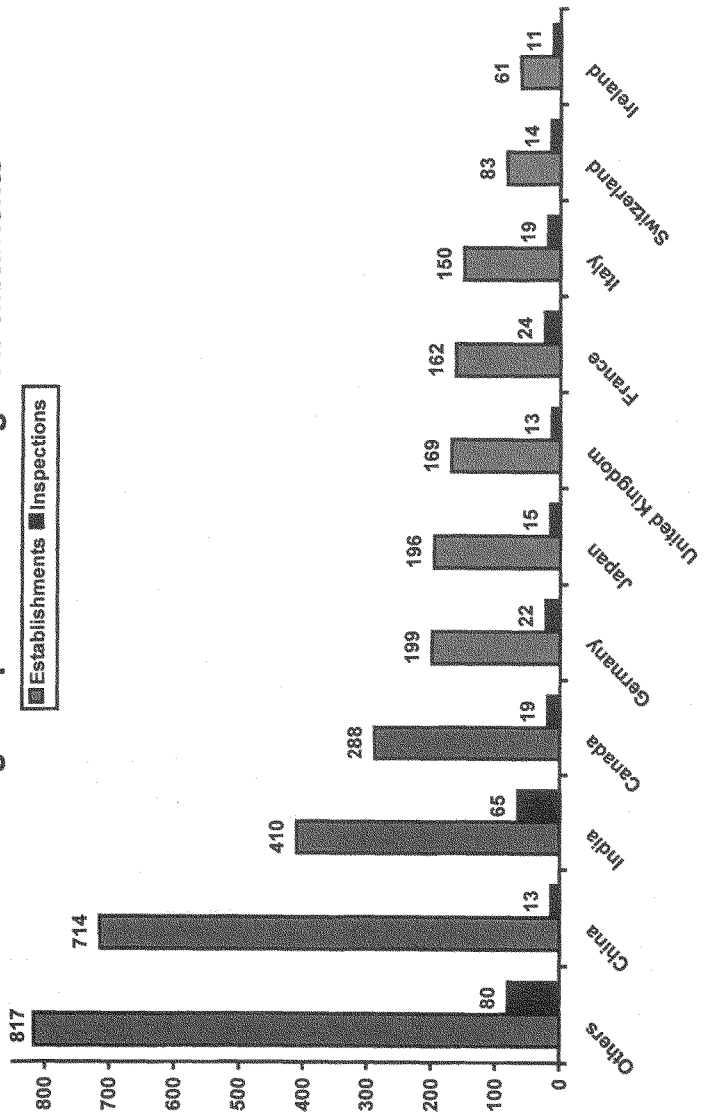
#4. Develop and establish a module in ORAU to complement the foreign inspection cadre training course.	Approved, ORA/DHRD action required
#5. Employees will be allowed to utilize an AWS and/or participate in the FWAP program for the first week upon return from the foreign inspection trip.	Approved, supervisory implementation necessary
#6. Establish a pilot for FY04 for Foreign Inspection GS-13 position for CSO/Analyst.	Approved, ORM action required
#7. An evaluation of implemented recommendations (new features) after 12 months.	Approved, initial date 10/1/03 to 9/30/04, DFI tasked with coordination with NTEU

Current Procedures and/or Changes to operations
#1. Up to fifteen (15) hours of overtime or compensatory time per week will be authorized in advance for workdays in excess of eight hours for all trips involving transoceanic travel. For all other trips (e.g., Canada and Mexico) employees will be authorized up to ten (10) hours per week for workdays in excess of eight (8) hours. All overtime must be requested and approved in advance.
#2. Annual leave may be approved at two days per week not to exceed a total of five days per trip, *provided that there is no additional cost to the government.*

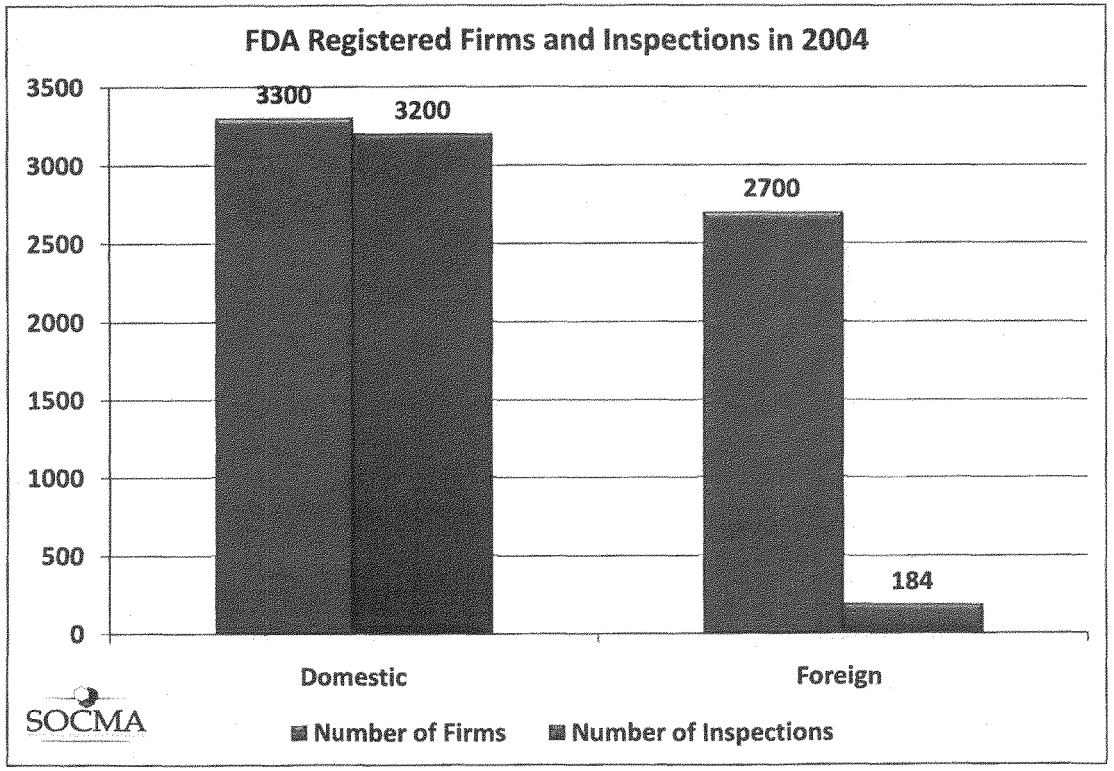
It is the decision of this office, in keeping with the recommendations of the VFI workgroup, that the accepted and approved incentives are applicable ONLY to qualified GS-11/12/13 members of the foreign inspection cadre and excludes employees who are participating in the GS-13 Pilot Program for Foreign Inspections.

Ex. #	Description	Date
1	Subcommittee on Oversight and Investigations Witness List	11/01/07
2	O&I Hearing Memo, subject: "FDA Foreign Drug Inspection Program: A System at Risk."	10/31/07
3	FDA Foreign Drug Inspection Program Figures	11/1/2007
4	Letter from Rep. Dingell, et al, to FDA Commissioner Andrew von Eschenbach, re: imported prescription drugs and the ingredients used in their manufacturing.	10/2/2007
5	Letter from Rep. Dingell, et al, to Commissioner von Eschenbach, re: FDA's oversight of foreign drug manufacturing facilities.	10/12/2007
6	Government Accountability Office (GAO) report, subject: "Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program."	Mar-98
7	"Petition to Request the FDA to Rank Foreign and Domestic Drug Manufacturing Firms Together for Purposes of the Agency's Risk-Based Approach to Inspections and Take Other Steps to Reduce the Public Health Risks Associated with Imported Drugs."	unspecified
8	European Fine Chemicals Group (EFCG) and the Synthetic Organic Chemical Manufacturers Association (SOCMA) Joint Position Paper, subject: "Uneven Enforcement Leads to Sub-par Drugs and National Security Risk."	8/22/2006
9	U.S. Embassy in India report, subject: "House Committee India Visit to Assess Improvements Needed in the Foreign Drug Inspection Program."	unspecified
10	21 USCS § 360 "Registration of Producers of Drugs and Devices."	8/13/2007
11	Form FDA 463 (2)	10/10/2007
12	Presentation by Deborah Autor, CDER Office of Compliance at the GPhA 2007 Fall Technical Conference, subject: "FDA Perspective: High Priority Topics & Future Directions."	10/10/2007
13	Email attachment from Heather Rubino Althouse, re: Drug Import Activities conducted by FDA's Office of Regulatory Affairs since FY02	unspecified
14	FDA Internal Report, Import Drug Program	1993
15	Washington Post article by Marc Kaufman, re: "FDA Scrutiny in India, China as Drugs Pour into U.S."	6/17/2007
16	U.S. News & World Report article by Nancy Shute, re: "Are Your Drugs Safe?"	10/15/2007

Exhibit 3

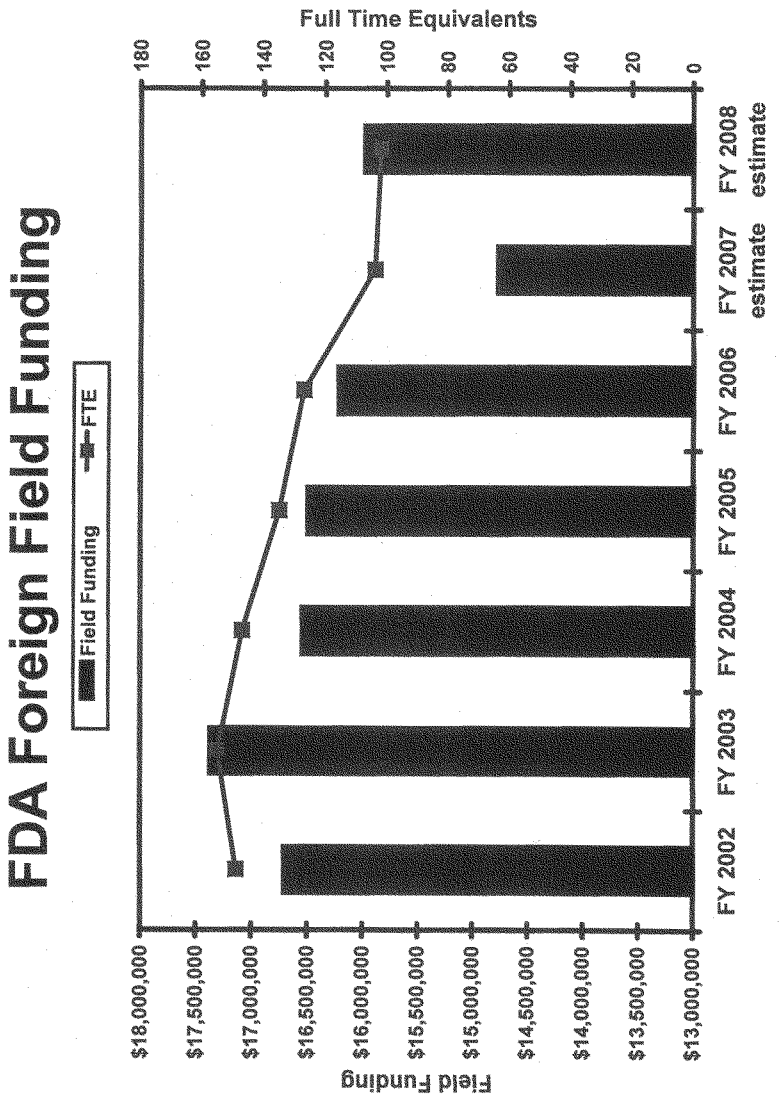


*GAO Testimony, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, November 1, 2007.



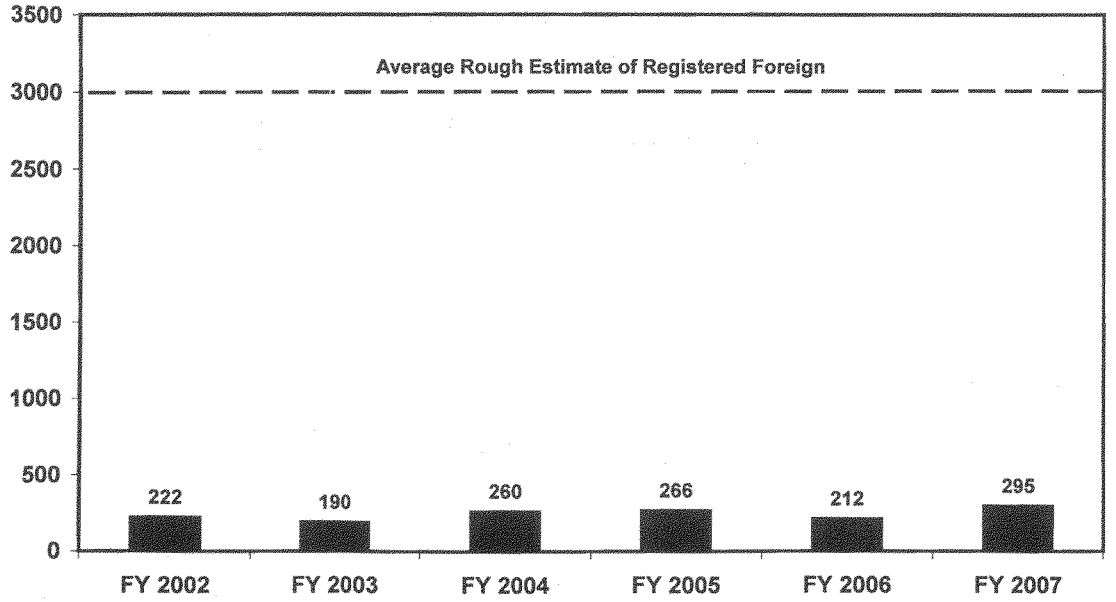
Number of firms data taken from the CDER 2005 Compliance Update presented by Kristen Evans at the 29th International cGMP Conference, University of Georgia, March 2005.

Number of inspections data taken from the 2004 CDER Report to the Nation published August 2005.



*FDA Data Provided to Committee on Energy and Commerce, October 2007

FDA Foreign Inspections
FY 2002 - 2007



*GAO Testimony, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, November 1, 2007.

Exhibit 4

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

October 2, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-0001

Dear Dr. von Eschenbach:

Under Rules X and XI of the Rules of the U.S. House of Representatives, the Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations are investigating the ability of the Food and Drug Administration (FDA) to protect the American public from excessive risks associated with imported prescription drugs and the ingredients that are used in their manufacture. As part of this investigation, Committee staff recently accompanied FDA staff on several foreign inspections in both China and India, which are major manufacturers and exporters of pharmaceutical products. We appreciate the cooperation we received from your agency to ensure that our staff could observe these inspections as well as your staff's assistance with our overall investigation.

The Committee examined the FDA's foreign drug inspection program nearly 10 years ago and identified a number of deficiencies. Unfortunately, many of these deficiencies appear to continue to plague the program today, and in some cases appear to be worse. For example, databases and computer systems used by FDA to track drug firms exporting to the U.S. still seem incapable of providing meaningful, real-time data regarding which firms are actively shipping products to the U.S. and when they were last inspected. Moreover, the amount of time between surveillance inspections appears inconsistent and, in some cases inspections are quite overdue. Finally, constraints on general resources appear to be having a direct effect on a several aspects of the program. This includes the ability to hire and use language interpreters so that FDA staff are not forced to use an interpreter provided by the drug firm being inspected; the length of time they can stay at a particular firm for an inspection; and the ability to do rapid follow-up inspections once problems are identified.

Given the limitation on these resources and the effect it is having on the program, coupled with the increasing growth in overseas drug manufacturers seeking to export products to U.S. markets, the Committee remains concerned about the overall capability of the FDA's foreign drug inspection program and its ability to keep up with a changing global marketplace. As the U.S. increasingly relies upon drug products from foreign manufacturers, it is critical that FDA have a robust capability to oversee foreign drug manufacturing facilities, which will clearly require significant re-tooling of this program. We believe your office should give this matter increased and immediate attention.

To date, Committee staff has attempted to both obtain basic data on FDA's foreign drug inspection program and its present workload obligations. This has included several meetings and conference calls with FDA officials responsible for managing this program. Perhaps because of the limitations and configurations of current FDA databases that provide information on drug imports, FDA has apparently experienced considerable difficulty in providing basic information to the Committee. These limitations include the inability to provide: (1) number of firms currently exporting to the U.S.; (2) when they were last inspected; (3) where they are located, and (4) projections of new firms seeking to export drug products to the United States. On August 23, 2007, Committee staff conducted a conference call with members of your staff to obtain a basic outline of data regarding FDA inspections of foreign drug product manufacturers. From that discussion, Committee staff understood your employees to represent the following information regarding FDA's present knowledge about foreign drug manufacturers that ship product to the U.S. (and other related inspection activities). Based on this, we request that your office confirm whether the following information is accurate, and that you supply additional information as requested:

1. As of August 23, 2007, there were 2,967 pharmaceutical product-manufacturing firms registered with the U.S. that are likely shipping to the U.S. and would be subject to: (a) pre-approval inspection; and (b) ongoing surveillance inspections.

2. Of these nearly 3,000 firms, they break down as follows: (a) 183 are making both dosage/active pharmaceutical ingredients (API) products; (b) 1,146 are making API only; (c) 1,036 are making dosage only; and (d) 600 firms are making products "unknown to the FDA." Please provide a description of what is meant by "unknown to FDA."

3. FDA has conducted approximately 1,379 foreign inspections since Fiscal Year 2002—1,196 were both pre-approval and current good manufacturing practice (CGMP) inspections, 107 were pre-approval inspections only, and 76 were CGMP inspections only.

4. Each year, FDA defines and identifies through its risk model approximately 100 "high risk" firms for CGMP surveillance inspection, but can only undertake about 25 such inspections annually due to resource constraints. Please provide the risk scores for the top 150 firms assessed by FDA's risk model for 2006 inspections.

5. FDA does not know the exact number of firms that currently manufacture and export over-the-counter (OTC) products to the U.S. or whether those firms have been inspected.

6. FDA databases do not provide full accounts of what is entering the U.S. at any given time and what is the present inspection workload. FDA is, however, working to update and "coordinate" these databases.

7. FDA is currently unable to easily distinguish between firms which are "registered" to ship to the U.S. and firms which are actually "shipping" to the United States.

Finally, we request additional information on the following questions:

1. Please provide a comprehensive list of all foreign companies that manufacture drug products, including OTC drugs, prescription drugs, and APIs, and the specific products each firm exports to the United States.

2. For each firm on this list, please provide: (a) where the company is located; (b) how long the firm has been exporting to the U.S.; and (c) when FDA last inspected the firm. Also, please identify which firms have undergone a New Drug Application or Abbreviated New Drug Application inspection (referred hereafter as a "pre-approval" inspection). Please further identify which of these firms have received a CGMP inspection and with what frequency.

3. Please provide a detailed description of the risk management model FDA currently uses to determine which foreign inspections to undertake.

4. How many foreign firms manufacture drug products for export to the U.S. but have never received an FDA inspection of any kind?

5. Pursuant to 21 USC 360(h), it is required that every *domestic* "establishment engaged in the manufacture, propagation, compounding, or processing of a drug" be inspected by the FDA at least once every two years. Does FDA inspect domestic firms once every two years? If not, which firms subject to the requirement are not inspected once every two years? If a subset of firms is identified in this category, please explain why they are not subject to an inspection once every two years.

6. What are the average differences in the frequency of inspections between foreign and domestic firms? Are there any difficulties for FDA in obtaining these data?

7. What statutory or regulatory requirements exist for FDA to inspect foreign drug manufacturing firms at a particular frequency?

8. In its 1998 report entitled "FDA: Improvements Needed in the Foreign Drug Inspection Program," the Government Accountability Office (GAO) found that FDA lacked a comprehensive, automated system for managing its foreign inspection program. At the

time, GAO observed that 15 different computer systems—very few of which were integrated—were used to manage FDA's foreign drug inspection program. Almost 10 years later, FDA officials have told staff that they still have considerable difficulty with the computer databases used to track and manage foreign inspections for those firms exporting drug products to the United States. What are the current limitations on FDA's ability to track drug exports sent to the U.S., and what limitations do the present systems have on managing foreign inspections? What action is FDA taking to strengthen this information technology?

9. Please provide a detailed description of the personnel structure for foreign inspections. How do foreign inspectors fit within FDA's Division of Field Investigations (DFI)? Who performs foreign inspections, and how many of these inspectors are there? How are inspections assigned? What are the requirements for inspectors to prepare for foreign inspections? Do they specialize in certain regions of the world?

10. Does FDA assess and work with foreign inspectorates to maximize the effectiveness of its foreign inspection program? Describe how FDA's DFI works with the Department of State to ensure an adequate level of in-country knowledge and support (e.g., for translations and logistics) for foreign inspections?

We appreciate your attention to this matter and look forward to working with you to address this important public health matter. We are requesting that you provide answers to these questions on a rolling basis, but no later than three weeks from the date of this letter. If you have any questions about this request, please contact us or have your staff contact Chris Knauer or Joanne Royce with the Committee Majority staff at (202) 226-2424 or Peter Spencer with the Committee Minority staff at (202) 225-3641.

Sincerely,

John D. Dingell
Chairman

Joe Barton
Ranking Member

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Ed Whitfield
Ranking Member
Subcommittee on Oversight and Investigations

Exhibit 5

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

October 12, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
5600 Fisher Lane, Room 1555
Rockville, MD 20857

Dear Dr. von Eschenbach:

As part of the Committee on Energy and Commerce's ongoing investigation into the ability of the Food and Drug Administration (FDA) to protect the American public from excessive risks associated with imported prescription drugs and the ingredients that are used in their manufacture, we recently sent you a request for information concerning FDA's oversight of foreign drug manufacturing facilities (see attached). The purpose of this letter is to outline observations from a recent Committee staff oversight trip to China and India, which was conducted to observe FDA inspections, as well as gather information from industry and regulatory officials in these countries. Information obtained from this investigative trip, in addition to previous and continuing work in this area, has raised a number of matters that warrant your attention.

We wish to emphasize at the outset that, based on Committee staff's observations and discussions with industry officials, the quality of the inspections appears both thorough and professional. As indicated below, however, there are several practical challenges faced by FDA teams that, if addressed, could enhance the agency's ability to conduct its overseas inspections. We understand that Committee staff has briefed you directly on some of the following observations, and we appreciate your prompt attention to these important issues. Nevertheless, we believe that these issues require a formal agency response so that we can better assess the assistance needed for FDA to build a stronger foreign-inspection program. Accordingly, under Rules X and XI of the Rules of the U.S. House of Representatives, we ask that you respond to the following requests by no later than the close of business two weeks from the date of this letter:

1. China and India have become major producers of active pharmaceutical ingredients and finished drug products. According to interviews with key Government and industry officials in both countries, China and India will continue to expand their production capability in these areas. There are already a number of multinational pharmaceutical

companies that have either located facilities in these two countries or plan to do so in the near future. Some of these companies are planning to market products directly within China and India, while others will use these facilities to manufacture and export pharmaceutical products to other countries, including the United States. This will likely pose significant additional workload requirements on FDA in the near future and will further strain an already-stretched FDA foreign inspection program. FDA needs to begin efforts to project what effect this additional workload will have (or is having) on the existing inspection program and determine the level of additional resources that will be needed, including inspectors willing to travel overseas. Please describe how FDA is assessing future workload requirements for its foreign inspection program. In addition, does FDA have any current projections of what the global marketplace in the area of pharmaceuticals will be like in the coming years or decade? If so, please provide any analysis, particularly for China and India.

2. Establishing permanent FDA offices in China and India could greatly facilitate the inspection process, according to certain industry and Government observers who were interviewed by Committee staff. Such an office could assist in coordination of FDA entry and movement within the country and allow for more seamless operations during and between inspections. In addition, these permanent offices could assist in improving collaboration between the United States and other countries by facilitating cross training of regulatory inspectors and standardizing procedures. Please provide your assessment of the value and feasibility of opening permanent offices in China and India.

3. According to Committee staff, senior Indian officials from that country's Government and drug industry have expressed support for having an FDA presence in India. Such presence could serve multiple goals. First, it could provide FDA with the ability to more rapidly inspect Indian firms, as needed, reducing logistical and long-distance travel burdens. Second, it could provide India's key regulatory agencies, which may soon undergo reform to build capability and capacity, with a better understanding of how FDA conducts current good manufacturing practice inspections. Finally, it would facilitate exchanges of information and practices regarding oversight of drug product safety in the growing Indian drug-manufacturing sector. Is FDA or the Department of Health and Human Services (HHS) working with India on any framework that would allow for a permanent presence in that country? If so, please provide details of this work to the Committee. If not, please explain why not, given India's prominence in the area of drug manufacturing and its apparent willingness to have an FDA presence within India.

4. It remains unclear what China's position is on the matter of an FDA office, although Chinese officials emphasized to Committee staff that they seek increased cooperation and collaboration with FDA. We understand that this is the subject of continuing discussions between senior HHS officials and their Chinese counterparts. In a related matter, we understand HHS and FDA are currently working on a Memorandum of Agreement with China regarding the regulation of drug imports. Please provide ongoing

briefings on efforts by FDA and HHS to work with the Chinese on any framework that involves drug inspections.

5. At a minimum, according to Committee staff, a Foreign Service National (FSN) employed by FDA at U.S. embassies in China or India could greatly facilitate travel logistics, independent translation services, and essential background information for FDA inspectors before and during inspections. FSNs dedicated to FDA teams could provide in-country expertise and support to the FDA inspection program until a more formal or elaborate arrangement is made by the United States and certain key host countries. Has FDA considered the use of FSNs in either country to help facilitate its inspection efforts? If so, please describe that effort. If not, is this an area that FDA would contemplate exploring?

6. According to Committee staff, Chinese language translators were provided to FDA teams by the companies being inspected. In general, FDA foreign inspections are technically complex and often confrontational. A translator hired by the company being inspected raises obvious conflicts of interest. It would appear that inspections conducted in certain parts of the world would benefit from translators who work directly for the U.S. Government. The State Department may be able to provide translators to the inspectors to facilitate impartial communications between FDA inspectors and the companies being inspected. Please describe FDA plans to employ U.S.-financed translators for foreign language-related inspections.

7. The current schedule of FDA inspections can require FDA teams to travel for three continuous weeks in order to conduct three inspections. Senior inspectors told Committee staff that this is a particularly demanding schedule that can compromise the quality of the inspections. In the United States, when problems are identified in a particular firm, FDA inspectors can remain additional days to complete their work. In the overseas arena, inspections are usually bundled together as a single trip—which may involve multiple countries. Given the complex travel logistics, FDA inspectors have no extra time to spend on a particular inspection. Has FDA done a cost-benefit analysis of these tightly scheduled, multi-firm, multi-country, multi-week trips? Would FDA be better served changing the structure of foreign inspection trips in order to reduce trip duration and to allow more time and flexibility on particular inspections if problems are found?

8. Committee staff observed that FDA inspectors did not receive briefings on the regulatory and political climate of the countries they entered. Briefings provided either directly by FDA or by the State Department could assist FDA inspectors to maneuver more easily within foreign countries. Moreover, it is our understanding that inspectors do not specialize in a particular country or region of the world, but instead may travel to any country where a firm is subject to an FDA inspection. Please describe whether you believe country-specific briefings would assist FDA inspection teams in conducting their work and, if so, how you plan to incorporate this into your foreign inspection program.

Moreover, please describe whether there would be an advantage for FDA inspectors to specialize in certain countries or regions.

9. Committee staff observed that FDA inspectors did not receive health briefings regarding disease risks in the countries they were entering, or what precautions should be taken to prevent potentially contracting diseases while in those countries. Diseases such as malaria and dengue are prevalent in many countries and pose significant health risks to FDA inspectors. Standardized health briefings would greatly enhance the ability of FDA teams to avoid illness and maintain the integrity of the foreign inspection program. In addition, it appears that FDA inspectors were not fully aware that the U.S. Embassy staff could assist with travel and health-related issues to FDA employees on official Government business. Please describe how FDA inspectors are briefed regarding disease threats in specific countries and what precautions FDA formally provides inspectors about guarding their health before they begin a foreign assignment. Also, please describe what contingency options are provided to FDA inspectors regarding travel and other extraordinary circumstances before they begin an assignment.

Thank you for your prompt attention to this matter. If you have any questions related to this request, please contact us or have your staff contact Christopher Knauer or Paul Jung of the Committee Majority staff at (202) 226-2424 or Peter Spencer of the Committee Minority staff at (202) 225-3641.

Sincerely,

John D. Dingell
Chairman

Joe Barton
Ranking Member

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Ed Whitfield
Ranking Member
Subcommittee on Oversight and Investigations

Attachment

Exhibit 6

United States General Accounting Office

GAO

Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives

March 1998

FOOD AND DRUG ADMINISTRATION

Improvements Needed in the Foreign Drug Inspection Program

GAO/HEHS-98-21

GAO

United States
General Accounting Office
Washington, D.C. 20548

Health, Education, and
Human Services Division

B-275814

March 17, 1998

The Honorable Joe Barton
Chairman, Subcommittee on Oversight and
Investigations
Committee on Commerce
House of Representatives

Dear Mr. Chairman:

In the late 1980s, at least 15 Americans reportedly suffered epileptic seizures, and 2 died, after taking a drug that allegedly contained a poor-quality ingredient that had been manufactured in a foreign country and imported by a U.S. pharmaceutical company. Reports of these tragic incidents and other problems raised concerns about the Food and Drug Administration's (FDA) ability to ensure the safety and quality of the increasing volume of foreign-produced drugs imported daily into the United States.

According to FDA, as much as 80 percent of the bulk pharmaceutical chemicals used by U.S. manufacturers to produce prescription drugs is imported. Moreover, the number of finished drug products manufactured abroad for the U.S. market is increasing. FDA inspects foreign manufacturers to help ensure that pharmaceutical products entering the United States are safe, pure, and high in quality.[1] However, a 1988 FDA internal review and a 1993 internal discussion paper identified serious problems with the agency's foreign inspection program.[2] Specifically, these internal evaluations found that FDA was not taking prompt action against foreign manufacturers because inspection reports were not being prepared in a timely manner. The 1993 discussion paper also noted that headquarters staff often disagreed with field investigators about the results of foreign inspections and whether FDA should reinspect problem manufacturers to verify that they had corrected serious deficiencies. Further, the evaluations found that FDA was not routinely inspecting foreign manufacturers to ensure that they complied with U.S. manufacturing standards. Finally, the evaluations found that FDA did not

[1]We use "pharmaceutical products" to refer to pharmaceuticals imported in finished dosage form as well as bulk drug substances (for example, active pharmaceutical ingredients or bulk pharmaceutical chemicals).

[2]Office of Regulatory Affairs, Program Evaluation Branch, "An Evaluation of FDA's Foreign Inspection Program," Rockville, Md., March 1988, and the internal FDA discussion paper entitled "Recommendations to Strengthen Surveillance and Enforcement Operations Associated with the Importation of Human Drugs," prepared by the Regional Director and senior staff, mid-Atlantic Region, 1993.

have a comprehensive data management system to monitor foreign manufacturers. The evaluations concluded that unless corrected, problems in FDA's foreign inspection program could lead to the importation of adulterated and low-quality drugs that could pose serious health risks to Americans.

This report responds to your request that we examine FDA's efforts to correct problems identified in the earlier evaluations. In subsequent discussions with your office, we agreed to examine FDA's efforts to

- prepare inspection reports and take enforcement actions against foreign pharmaceutical manufacturers in a timely manner,
- improve the consistency with which FDA evaluates the results of foreign inspections and conducts reinspections to verify that foreign pharmaceutical manufacturers have corrected serious deficiencies,
- conduct routine inspections of foreign pharmaceutical manufacturers to monitor their compliance with U.S. quality standards, and
- improve the management of data needed for planning inspections, monitoring inspection results, and taking enforcement actions.

To obtain information on FDA's foreign inspection program, we interviewed FDA officials and examined documents regarding FDA's requirements for inspecting, reporting, and taking enforcement actions against foreign pharmaceutical manufacturers. We also examined FDA's 1988, 1993, and 1997 internal evaluations of its foreign inspection program and discussed them with agency officials.[3]

To determine the timeliness of enforcement actions, the consistency of evaluations of foreign inspection results and enforcement actions, the frequency of routine inspections, and the management of data, we analyzed computerized data on the 287 foreign inspection reports FDA reviewed during fiscal year 1996 and the 257 it reviewed during fiscal year 1997. In addition, we reviewed inspection reports for 22 pharmaceutical manufacturers in China and 17 in India that were inspected between January 1, 1994, and May 15, 1996. We focused on China and India because they represent two developing countries that had large increases in pharmaceutical products exported to the United States. We interviewed the investigators who conducted the inspections and the FDA officials responsible for reviewing these inspection reports. We did not independently verify the accuracy of data provided by FDA. These are the

[3]Office of the Commissioner, U.S. Food and Drug Administration, "Summary Report of the Foreign Inspection Working Group," Rockville, Md., June 1997.

same data FDA uses to manage the foreign inspection program. Except for this, we performed our work from April 1996 to February 1998 in accordance with generally accepted government auditing standards.

Results in Brief

FDA has taken several actions to address problems with its foreign inspection program that were identified in two previous internal evaluations. Although FDA has improved the timeliness with which investigators submit inspection reports, in fiscal year 1996, almost 60 percent were still submitted later than called for by agency standards, including half the reports that identified the most serious deficiencies in manufacturing quality. Moreover, FDA is still experiencing delays in taking prompt enforcement action against foreign pharmaceutical manufacturers. During fiscal year 1996, FDA took, on average, almost four times longer than its required time to issue warning letters to foreign pharmaceutical manufacturers with serious manufacturing deficiencies. The extent of these delays can be significant. For example, in one case FDA allowed a manufacturer in India to continue exporting its pharmaceutical products to the United States despite its investigator's finding that the manufacturer could not adequately test for impurities in its product and water system. Nearly 2 years elapsed before FDA determined that enforcement action had not been taken against this manufacturer.

During fiscal years 1996 and 1997, headquarters review personnel continued to downgrade the classifications of inspections recommended by its field investigators who conducted the inspections. Most of the decisions to downgrade the classifications were based on foreign manufacturers' promises to implement corrective actions. As a result, FDA conducted fewer reinspections of these facilities to verify that foreign manufacturers had corrected serious manufacturing deficiencies. In one case, for example, FDA headquarters reviewers accepted a manufacturer's written explanation of the actions it was taking to correct deficiencies in its testing procedures, instead of issuing the manufacturer a warning letter. As a result, this facility was not reinspected even though agency documents raised questions about the manufacturer's trustworthiness. Our analysis showed that in fiscal year 1996, half of the inspections in which field investigators recommended agency enforcement action were downgraded by headquarters review staff, which meant that FDA conducted 50 percent fewer reinspections to verify that foreign manufacturers corrected the deficiencies observed during their initial inspections. The frequency of downgrades has increased significantly in the past year. In fiscal year 1997, FDA downgraded about two-thirds of the

inspections in which field investigators recommended agency enforcement action.

FDA conducts infrequent routine inspections of foreign manufacturers to ensure that they continue to comply with U.S. quality standards, although routine surveillance inspections constitute FDA's most comprehensive program for monitoring the quality of marketed pharmaceutical products. Most inspections of foreign pharmaceutical manufacturers are performed to approve the marketing of new products. Routine surveillance inspections of manufacturers producing approved pharmaceutical products already marketed in the United States accounted for only 20 percent of FDA's foreign inspections during fiscal year 1995. As a result, routine inspections of foreign pharmaceutical manufacturers occur with far less frequency than the 2-year interval required for domestic manufacturers. In China and India, for example, 4 to 5 years elapsed between FDA inspections of pharmaceutical manufacturers. Acknowledging that it needs to conduct more routine surveillance inspections, FDA has developed a four-tier strategy aimed at ensuring that high-risk foreign pharmaceutical products and manufacturers are inspected more frequently. While this strategy may improve the frequency of routine inspections for some facilities, FDA acknowledges that most foreign pharmaceutical manufacturers may never receive a routine surveillance inspection.

FDA has been striving to improve its management of data needed for planning inspections, monitoring inspection results, and taking enforcement actions. At present, FDA relies on 15 separate systems to identify foreign pharmaceutical manufacturers, plan foreign inspection travel, track inspection results, and monitor enforcement actions. As a result, essential foreign inspection data are not readily accessible to the different FDA units that are responsible for planning, conducting, and reviewing inspections and taking enforcement actions against foreign manufacturers. FDA is developing a comprehensive, agencywide automated system to provide better data for managing its foreign inspection program. The first phase of FDA's new Field Accomplishments and Compliance Tracking System (FACTS) is expected to be implemented during fiscal year 1998.

Our report contains several recommendations to the Commissioner of FDA to establish procedures to help ensure timely compliance with U.S. quality standards by foreign pharmaceutical manufacturers.

Background

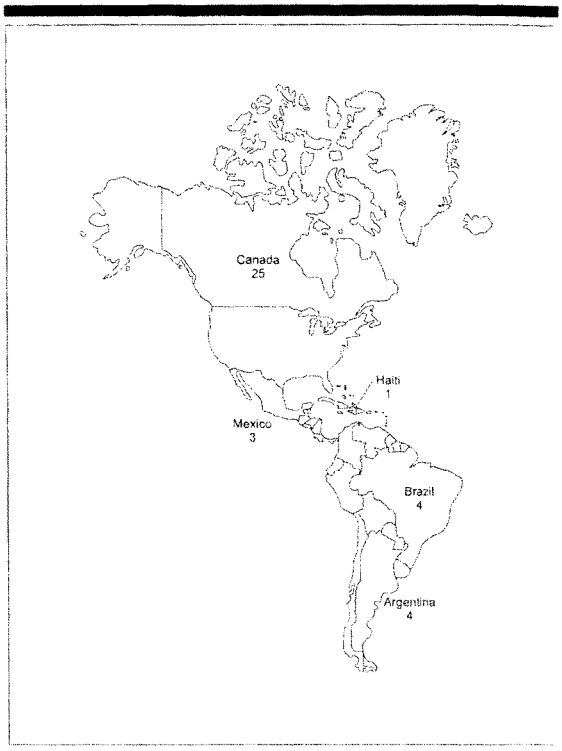
FDA is responsible for the safety and quality of domestic and imported pharmaceutical products under the Federal Food, Drug, and Cosmetic Act. Specifically, FDA's Center for Drug Evaluation and Research (CDER) establishes standards for the safety, effectiveness, and manufacture of prescription pharmaceutical products and over-the-counter medications. CDER reviews the clinical tests and manufacture of new pharmaceutical products before they can be approved for the U.S. market, and it regulates the manufacture of pharmaceutical products already being sold to ensure that they comply with federal statutes and regulations, including current "good manufacturing practice" (GMP). GMP requirements are federal standards for ensuring that pharmaceutical products are high in quality and produced under sanitary conditions.[4] In addition, CDER enforces the act's prohibitions against the importation of adulterated, misbranded, and counterfeit pharmaceutical products.

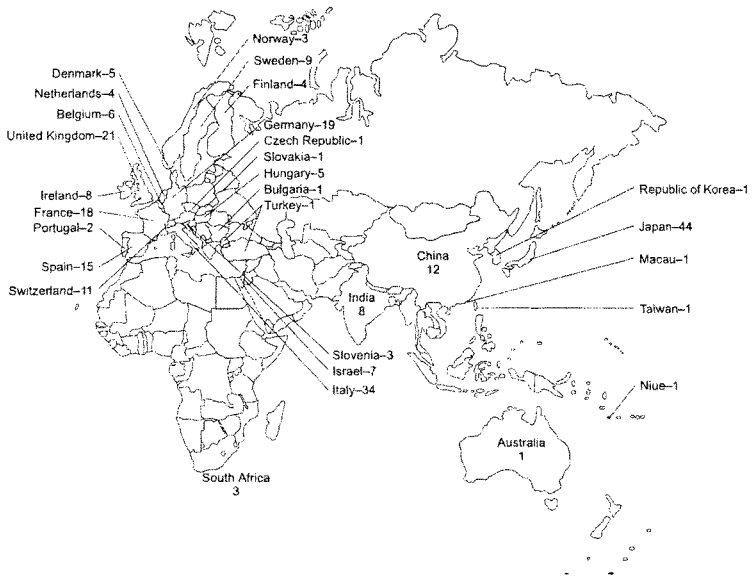
CDER regulates the manufacture of pharmaceutical products by requesting that FDA's Office of Regulatory Affairs (ORA) inspect manufacturers both at home and abroad to ensure that pharmaceuticals are produced in conformance with GMPs. ORA manages investigators located in FDA's 21 district offices. Approximately 375 investigators and 75 microbiologists and chemists conduct inspections of foreign pharmaceutical manufacturers. ORA's investigators inspect manufacturers that produce pharmaceuticals in finished form as well as manufacturers that produce the active ingredients used in finished pharmaceutical products. Typically, ORA investigators travel abroad for about 3 weeks at a time during which they inspect approximately three manufacturers. Each inspection ranges from 2 to 5 days in length, depending on the number and types of products inspected.[5] In fiscal year 1996, FDA reviewed the results of 287 inspections of foreign pharmaceutical manufacturers conducted by its investigators in 35 countries (see figure 1). About 70 percent of these inspections were performed in manufacturing facilities that produce the active ingredients used in finished pharmaceutical products.

[4]The current good manufacturing practice regulations (21 C.F.R. parts 210 and 211) provide a framework for manufacturers to follow to ensure that they produce safe, pure, and high-quality pharmaceutical products. While FDA has an essential role in ensuring safe, pure, and high-quality pharmaceutical products, the individual manufacturers are ultimately responsible for the safety and quality of their products.

[5]FDA contends that foreign inspections now range from 2 to 7 days and may be performed by a single investigator or an inspection team.

Figure 1: The 287 FDA Inspections of Foreign Pharmaceutical Manufacturers in 35 Countries Reviewed During Fiscal Year 1996



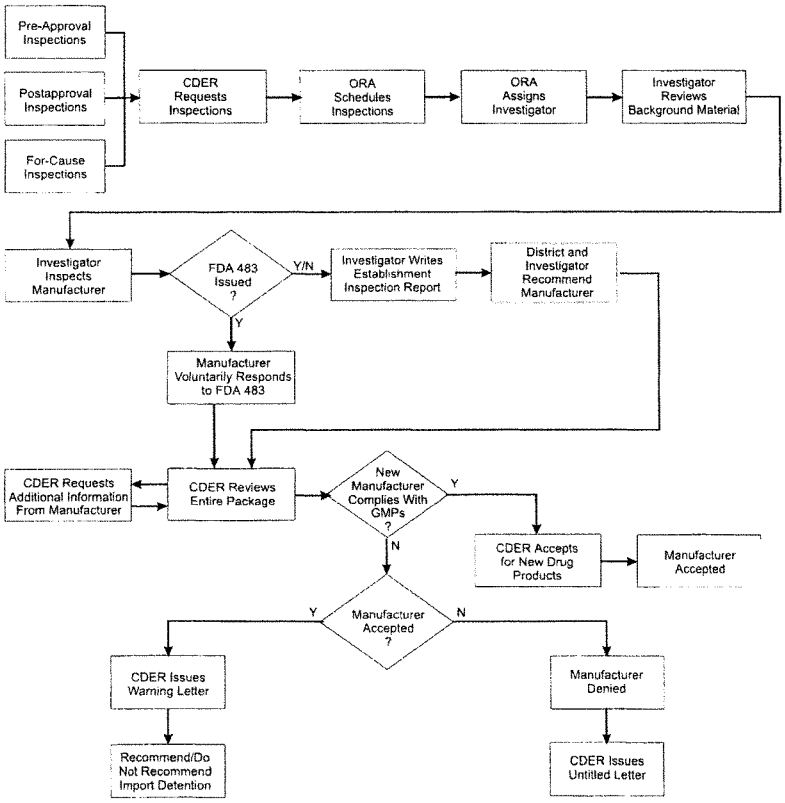

Norway–3
Sweden–9
Finland–4
Denmark–5
Netherlands–4
Belgium–6
United Kingdom–21
Germany–19
Czech Republic–1
Slovakia–1
Hungary–5
Bulgaria–1
Turkey–1
Ireland–8
France–18
Portugal–2
Spain–15
Switzerland–11
Slovenia–3
Israel–7
Italy–34
China
12
India
8
Republic of Korea–1
Japan–44
Macau–1
Taiwan–1
Niue–1
Australia
1
South Africa
3

CDER requests that ORA's investigators conduct inspections for three reasons. First, CDER requests pre-approval inspections to ensure that before a new drug application is approved, the manufacturer of the finished pharmaceutical product as well as each manufacturer supplying a bulk pharmaceutical chemical used in the finished pharmaceutical product comply with GMPs. Each step in the manufacture and processing of a new drug, from the sources of raw materials to final packaging must be approved by FDA. Second, CDER requests postapproval or routine surveillance inspections to periodically assess the quality of marketed pharmaceutical products. During these inspections, investigators verify that manufacturers of finished pharmaceutical products and bulk pharmaceutical chemicals comply with GMPs.[6] Third, CDER requests for-cause inspections when it receives information indicating problems in the manufacture of approved pharmaceutical products. In addition, CDER requests for-cause inspections of manufacturers that were not in compliance with GMPs during previous inspections. In for-cause inspections, FDA investigators determine whether the manufacturer has improved its production processes to comply with GMPs.

During an inspection, the ORA investigator examines the pharmaceutical manufacturer's production processes, product packaging and labeling processes, product contents, warehouse practices, quality control, laboratories, recordkeeping systems, and other manufacturing practices. The investigator reports observations of significant objectionable conditions and practices that do not conform to GMPs on the list-of-observations form, commonly referred to as FDA form 483. At the end of the inspection, the investigator gives a copy of the form 483 to the highest ranking management official present at the manufacturing facility. The investigator also discusses the observations on the form 483 with the firm's management to ensure that they are aware of any deviations from GMPs that were observed during the inspection and suggests that the manufacturer respond to FDA in writing concerning all actions taken as a result of the observations. Figure 2 shows FDA's process for managing foreign pharmaceutical inspections.

[6]FDA's surveillance of foreign pharmaceutical products also includes routine sampling of imports at the port of entry to the United States. In addition, FDA's postapproval surveillance system for human pharmaceutical products consists of inspections of manufacturing establishments, which we discuss in this report.

Figure 2: How FDA Manages Foreign Pharmaceutical Inspections



After returning to the district office, the investigator prepares an establishment inspection report that describes the manufacturing operations observed during the inspection and any conditions that may violate federal statutes and regulations. The investigator also recommends whether the manufacturer is acceptable to supply pharmaceutical products to the United States. The investigator's district office formally endorses the recommendation after reviewing the inspection report to determine if it supports the proposed recommendation. The district office forwards its endorsement along with the investigator's establishment inspection report and the form 483 to CDER. The foreign inspection team within CDER's Office of Compliance reviews the documentation and the manufacturer's written response to FDA about any corrective actions taken. CDER then decides whether the manufacturer complies with GMPs.

Inspections of pharmaceutical manufacturers are classified in one of three categories. As table 1 shows, during fiscal year 1996, 238 inspections (or 83 percent) revealed deviations from GMPs. Of these, CDER determined that 46 inspections revealed deviations from GMPs that ranked in the most serious (or "official action indicated") category.

Table 1: Distribution of Inspection Results of Foreign and Domestic Pharmaceutical Manufacturers, Fiscal Year 1996

		Foreign		Domestic	
Classification	**Explanation**	**Number**	**Percent**	**Number**	**Percent**
Official action indicated (OAI)	OAI classifications are considered the most serious and indicate deviations from GMPs that require some FDA intervention to ensure that corrections are made. OAI classifications require FDA to issue either a warning letter or an untitled letter, the manufacturer to correct problems and respond in writing to FDA about the corrections made, and FDA to reinspect the manufacturer to verify that it has improved its production processes to comply with GMPs.	46	16%	182	21%
Voluntary action indicated (VAI)	VAI classifications are considered less serious than OAI classifications and indicate deviations from GMPs that are amenable to corrective [illegible] by the manufacturer with no compromise to safety. VAI classifications require the manufacturer to agree to correct problems and FDA to verify that it has corrected all less-serious deficiencies during the next routine surveillance.	92	67	328	38
No action indicated (NAI)	NAI classifications indicate that no deviations from GMPs.	[illegible]	17	342	40
Total		**287**	**100%**	**852**	**99%**

[illegible]FDA could not determine an inspection classification for 16 domestic inspections.

When CDER classifies a foreign pharmaceutical inspection as "official action indicated" (OAI), it sends the manufacturer an enforcement letter. CDER issues two types of enforcement letters: untitled letters and warning letters. CDER issues an untitled letter to a foreign manufacturer when the inspection was conducted as part of its review of a new drug application and the manufacturer has not previously been inspected and accepted to supply approved pharmaceutical products to the United States. The untitled letter notifies the manufacturer that its manufacturing process does not comply with federal statutes and regulations and that failure to take corrective action may result in the disapproval of any new drug application on which the manufacturer is listed.

CDER issues a warning letter to a foreign manufacturer when a subsequent inspection of its facility is classified as OAI. Warning letters are issued to manufacturers that are already supplying approved pharmaceutical products to the United States. Warning letters indicate that serious manufacturing deficiencies can and are affecting commercially marketed

products. The warning letter notifies the manufacturer of its violation of federal statutes and regulations and that failure to take corrective action may result in further FDA enforcement action. CDER issued 17 untitled letters and 19 warning letters to foreign pharmaceutical manufacturers in fiscal year 1996.

If CDER classifies an inspection as OAI and believes the manufacturer's product is adulterated because it was not produced in compliance with GMPS, CDER can instruct the district offices to cooperate with the U.S. Customs Service in detaining the manufacturer's product when it is offered for entry into the United States. In such a situation, the warning letter may also threaten to detain the manufacturer's products at U.S. entry points or notify the manufacturer that detention will occur. Customs, which controls the points where foreign shipments enter the United States, ensures that adulterated pharmaceutical products are either exported from the United States or destroyed. In fiscal year 1996, CDER determined that the pharmaceutical products made by two foreign manufacturers should be detained.

Timeliness of Inspection Reports Has Improved, but Delays in Taking Prompt Enforcement Actions Continue

FDA's 1988 internal evaluation found that delays in the submission of final inspection reports by investigators made it difficult for FDA to take prompt enforcement action against foreign manufacturers that did not comply with federal regulations that ensure the safety, purity, and quality of pharmaceutical products. Since then, FDA has taken several actions that have reduced the average time required by investigators to submit foreign inspection reports to headquarters. Despite this improvement, only about a quarter of the warning letters FDA issued in fiscal year 1996 to foreign pharmaceutical manufacturers found to have serious deficiencies met FDA's timeliness standards. The lack of prompt enforcement action may impair FDA's ability to prevent foreign manufacturers from exporting contaminated or adulterated pharmaceutical products to the United States.

FDA Has Acted to Improve the Timeliness of Enforcement Actions

FDA's 1988 internal evaluation of its foreign inspection program reported that the average length of time required from the completion of an inspection to CDER's receipt of a final report was slightly more than 3 months. Delays in submitting inspection reports may hinder CDER's ability to initiate timely enforcement actions to prevent contaminated or adulterated products from entering the United States. To reduce these

delays, the evaluation recommended that FDA explore new ways of processing inspection reports.

To strengthen its enforcement strategy, FDA revised its timeliness standards for new drug applications in October 1991 by requiring investigators and districts to submit all inspection reports classified as OAI or "voluntary action indicated" (VAI) to CDER within 30 work days of completing inspections.[7] FDA also revised its enforcement policy to require CDER to review OAI inspection reports containing recommendations for warning letters and issue the letters within 15 work days.

According to FDA officials, additional changes were made to help investigators submit more timely inspection reports on foreign manufacturers. In the early 1990s, FDA reduced the length of foreign inspection trips from about 6 to 3 weeks as well as the number of inspections an investigator conducted during the trip. The agency also revised inspection requirements for international travel to build time into foreign inspections for investigators to prepare their reports and provided investigators with notebook computers so that they could begin preparing their reports overseas.

Inspection Reports Are More Timely, but Many Miss FDA's Reporting Deadline

Although FDA has reduced the average time it takes to submit reports after inspections are completed from slightly more than 3 months to 2, over half of the reports in fiscal year 1996 did not meet FDA's timeliness standard. Our analysis of 287 foreign inspection reports CDER reviewed during fiscal year 1996 showed that about 42 percent (102) of the inspections that identified GMP deficiencies (either OAI or VAI) were submitted on time or within 30 work days of completing inspections. However, 58 percent (141) of the inspection reports were not timely (see table 2).[8]

[7]The same timeliness standards were extended to approved drug products in September 1994.

[8]Investigators classified an additional 44 inspections as not requiring any action by FDA or foreign manufacturers because insignificant or no deviations from U.S. GMPs had been observed.

Table 2: Work Days Between the Completion of Foreign Inspections and Submission of Inspection Reports to CDER, Fiscal Year 1996

	Inspection classifications recommended by investigators and districts			
Submitted to CDER (in work days)	Official action indicated	Voluntary action indicated	Total	Percent
30 days or less	41	61	102	42%
31- 60 days	37	79	116	48
61-90 days	4	14	18	7
91-120 days	0	3	3	1
121 days or more	0	4	4	2
Total	**82**	**161**	**243**	**100%**

About half of the inspections with the most serious deficiencies (classified as OAI or requiring official action) were submitted on time and half were not. Most of the OAI inspection reports that were submitted to CDER after the 30-day deadline were submitted within 60 work days. CDER received about one-third of the inspection reports with less serious deficiencies (classified as VAI, allowing foreign manufacturers to voluntarily make corrections) on time; two-thirds were late.

FDA reported more recently that its analysis of fiscal year 1997 data showed a modest improvement in the submission times for OAI and VAI inspection reports. FDA reported that in its analysis of 230 foreign inspection reports reviewed during fiscal year 1997, about 47 percent (75) of the inspections that identified GMP deficiencies (either OAI or VAI) were submitted on time. However, 53 percent (85) of the inspection reports were not timely.

Our review of inspection reports for China and India showed that regardless of the seriousness of the GMP deficiencies found, CDER did not receive the majority of the inspection reports within the 30-work day requirement. Specifically, 22 of the 36 OAI and VAI inspection reports (61 percent) we reviewed for China and India were not submitted on time.[9]

Although there was no one reason for the late submissions, CDER officials told us that an investigator may return to the United States 3 weeks after conducting his first inspection, making it impossible for him or her to submit an inspection report within 30 work days. Some investigators told us that the paperwork, which includes preparing numerous documents and exhibits to support the deficiencies observed, is time-consuming. In

[9]Three of the inspection reports we reviewed did not identify any deviations from U.S. GMPs.

addition, after returning to their district offices, some investigators stated that they are often confronted with competing demands on their time, such as responding to problems with domestic pharmaceutical manufacturers.

FDA Enforcement Actions Still Take Too Long

Although FDA established a 15-work-day standard for issuing warning letters, about one out of four warning letters issued by CDER during fiscal year 1996 was issued on time. The extent of these delays can be significant. For example, CDER took 4 months (80 work days) to issue a warning letter to one Chinese manufacturer inspected in September 1994. In the inspection report, received by CDER 2 months after the inspection, the investigator noted 20 significant deviations from U.S. GMPs and wrote that the manufacturer was incapable of producing the injectable pharmaceutical product for which it was seeking approval. The investigator wrote that "Virtually all of the processing equipment for the first phases of processing is filthy, in [an] extreme state of disrepair, and was removed during this inspection." Despite the severity of the inspection findings, it was not until March 1995 that CDER sent a warning letter to the manufacturer.

As shown in table 3, it took more than 15 work days to issue 23 of the 30 warning letters sent to foreign pharmaceutical manufacturers. After receiving the inspection reports from investigators, it took CDER between 21 and 148 work days to issue the 23 late warning letters, with an average of 57 work days. According to a CDER official, CDER experienced staffing shortages during the period we examined that delayed the review of incoming foreign inspection reports.

Table 3: Work Days Between CDER's Receipt of Inspection Reports and Issuance of Warning Letters, Fiscal Year 1996

Issued by CDER (in work days)	Number of warning letters issued	Percent
15 days or less	7	23%
16-30 days	6	20
31-45 days	5	17
46-60 days	2	7
61-75 days	3	10
76-90 days	3	10
91-105 days	2	7
106 or more days	2	7
Total	**30**	**101%**[a]

[a]Total does not add to 100 because of rounding.

More recently, FDA reported that its analysis of fiscal year 1997 data showed a substantial improvement in the time CDER spent in processing warning letters. FDA reported that 30 percent or 3, of the 10 warning letters issued to foreign pharmaceutical manufacturers during fiscal year 1997 were sent within 15 work days. On average, FDA issued the 10 warning letters in about 24 work days. However, compared with the number of warning letters issued during fiscal year 1996, FDA issued two-thirds fewer warning letters during fiscal year 1997.

Our analysis of inspections conducted in China and India between January 1, 1994, and May 15, 1996, showed that CDER did not issue any of the six warning letters within the agency's 15-work-day standard. The number of work days from CDER's receipt of inspection reports to the issuance of these warning letters ranged from 24 to 86 days, with an average of 40 days.

In one case, a February 1994 inspection of a plant in India making an antibacterial agent identified serious problems, including failure to ensure that the proper manufacturing process was followed and inadequate testing of impurities in the product and water used by the plant. The investigator also found that two deficiencies identified during a 1985 FDA inspection had not been fully corrected to meet U.S. quality standards.[10] Given the significance of the deficiencies found during the 1994 inspection, the investigator and his district office recommended that CDER

[10]During a 1994 inspection, FDA found that the manufacturer had not packaged stability samples of its product in simulated market containers as agreed and had implemented laboratory procedures for impurity testing that did not meet U.S. GMPs.

(1) not approve the new drug application, (2) advise FDA district offices to deny entry into the United States of any pharmaceutical products from this manufacturer, and (3) pursue additional enforcement actions against pharmaceutical products from the manufacturer that were already distributed in the United States. Notwithstanding the seriousness of the problems or the recommended enforcement action, it took 2 years for CDER officials to determine that they had not taken any enforcement action against this foreign manufacturer.

While CDER officials agreed with the district recommendation and planned to issue a warning letter, the letter was never sent to this foreign pharmaceutical manufacturer because CDER lost track of it during staffing changes. In March 1996, CDER officials determined that they had allowed this foreign manufacturer to continue shipping already approved bulk pharmaceutical products to the United States, even though the inspection had identified manufacturing problems such as unacceptable impurity testing procedures, no periodic review of the production process, and the failure to investigate product yields that were lower than the specified amount.[11]

In another case, it took CDER about 3 months to issue a warning letter to a foreign pharmaceutical manufacturer operating with 17 serious GMP deficiencies. FDA inspected this foreign manufacturer in April 1995, after receiving several new drug applications listing the manufacturer as a supplier of bulk pharmaceutical chemicals for use in U.S. finished drug products. The investigator found that the manufacturer did not have an appropriate impurity testing system and identified questionable results from impurity testing. The investigator believed that these questionable results represented a deliberate attempt to conceal instances in which the pharmaceutical products contained higher levels of impurities than permitted by U.S. standards. As a result, the investigator and his district office recommended that CDER not approve the new drug applications and that it issue a warning letter to the manufacturer.

Notwithstanding the serious nature of the investigator's findings, it took ORA about 2 months to submit the inspection report to CDER and another month for CDER to review the report. On August 1, 1995, slightly more than 3 months after the inspection, CDER issued a warning letter stating that it would not approve any applications listing this foreign pharmaceutical manufacturer as a supplier. During the time it took CDER to act on the

[11]According to FDA, a reinspection of this manufacturer found that it had implemented promised corrections and was in compliance with U.S. GMPs.

serious deficiencies and possible fraud identified by the investigator, a U.S. finished-drug manufacturer discovered that several containers labeled as a bulk pharmaceutical chemical product from the same foreign manufacturer contained an herbicide rather than a bulk chemical.

FDA Verifies Corrective Actions in Only About Half the Cases in Which Serious Deficiencies Are Identified

Members of the Congress and industry representatives have been concerned about the consistency of FDA inspections and subsequent enforcement actions taken against domestic and foreign pharmaceutical manufacturers. In FDA's 1993 internal evaluation, these concerns were attributed to differences in how field investigators and headquarters staff evaluated foreign inspection results and determined the appropriate follow-up activity. Moreover, the internal evaluation acknowledged that there was a perception that FDA relied on foreign facilities to correct manufacturing deficiencies because there were insufficient resources to conduct follow-up inspections to confirm that corrective actions had been implemented.

Our analysis of the foreign inspection reports reviewed during fiscal year 1996 showed that in about half the instances in which field staff concluded that the severity of inspection findings warranted a reinspection, headquarters disagreed. For domestic manufacturers with a history of serious GMP manufacturing problems, FDA typically conducts a reinspection to verify that promised corrective actions have been implemented. However, current FDA policy does not address the need for verifying the corrective actions of foreign pharmaceutical manufacturers in instances in which FDA headquarters downgrades the severity of inspection findings. As a result of downgrading, FDA conducted far fewer reinspections of foreign manufacturers than was recommended by its investigators. Without reinspections, FDA cannot adequately verify that foreign manufacturers have corrected serious deficiencies that could affect the safety, purity, and quality of their pharmaceutical products.

FDA's 1993 Internal Review Identified Differences in the Evaluation of Inspection Findings That Affected the Frequency of Reinspections

In the 1993 internal discussion paper, FDA managers found that agency headquarters' personnel downgraded the severity of the manufacturing deficiencies identified in foreign inspections and the need for reinspecting violative foreign manufacturers. However, they stated that FDA did not downgrade the severity of inspection findings for domestic manufacturers that had similar deficiencies. According to the review, this was caused by different FDA units being responsible for reviewing and evaluating inspection results and planning reinspections of foreign and domestic

pharmaceutical manufacturers to verify corrective actions. The discussion paper identified several instances in which approval of new drug applications was withheld, based on significant GMP deficiencies discovered during domestic inspections, whereas similar deficiencies found at foreign manufacturing facilities resulted in the approval of applications.

In the discussion paper, FDA managers stated that differences between the evaluations of foreign and domestic inspection results existed for two reasons. First, unlike for domestic inspections, decisions regarding the severity of the manufacturing deficiencies identified during foreign inspections are made by CDER staff rather than by the field investigators who actually conducted the inspections and their district office managers who endorse their recommendations. Second, they indicated that a perception existed that FDA has too few resources to conduct a reinspection of a foreign manufacturer to verify that corrections have been made. According to the review, this leads CDER staff to "trust" a foreign manufacturer to correct serious manufacturing deficiencies. The review described several instances in which significant GMP deficiencies at foreign facilities received little or no enforcement action, while similar deficiencies at domestic facilities resulted in product recalls or application denials.

To correct this problem, the discussion paper recommended that district offices, where the investigators are located, rather than CDER be responsible for evaluating the results of foreign inspections and determining the appropriate enforcement action, including the need for reinspecting the manufacturer. FDA officials disagreed with the assertion that its inspection and enforcement programs were applied disparately to domestic and foreign pharmaceutical manufacturers. Further, they argued that district offices already had this responsibility.

CDER Often Downgrades Investigators' Recommended Classifications of Inspection Findings

Our analysis of FDA computer data of foreign inspection reports reviewed during fiscal year 1996 showed that CDER and field investigators often disagree on the classification of inspection findings and the severity of the enforcement action that should be taken against foreign pharmaceutical manufacturers when GMP deficiencies are found. For 82 of the 287 foreign inspections reviewed during this period, field investigators concluded that the severity of the GMP deficiencies they observed warranted that CDER initiate official action against the manufacturers. The investigators' district offices also endorsed their classifications of these inspections and their

recommendations for enforcement action before these were forwarded along with the inspection reports and the form 483s to CDER. However, CDER officials downgraded the inspection classifications and recommendations for enforcement action in 41 of these inspections, based on foreign manufacturers' promises to implement corrective actions. CDER officials decided that rather than OAI, 40 of these inspections should be classified as VAI and 1 should be classified as "no action indicated" (NAI). Conversely, CDER officials upgraded the field investigators' classifications and recommendations for enforcement action in 11 foreign inspections and classified them OAI rather than VAI.

In instances in which inspections found serious GMP deficiencies but CDER downgraded the inspection classifications, FDA's procedures allow foreign manufacturers to continue exporting pharmaceutical products to the United States without reinspections to evaluate whether they comply with U.S. quality standards. The classification of an inspection determines to a large degree whether a reinspection is conducted. The OAI classification is the most serious and requires FDA to reinspect the manufacturer to verify that it has improved its production processes to comply with GMPs. When CDER does not accept the investigators' recommendations and classifies inspections as VAI rather than OAI, foreign manufacturers are allowed to voluntarily correct their deficiencies and respond in writing to FDA about the corrections made.[12] FDA officials have acknowledged that they sometimes base their downgrades of inspection classifications and approvals of new drug applications on foreign manufacturers' promises to implement corrective actions. They contend that during the next inspection, whenever it may be, FDA confirms that the corrections were made.

Our analysis of FDA computer data of foreign inspection reports reviewed during fiscal year 1997 showed that CDER and field investigators continue to disagree on the classification of inspection findings and the severity of the enforcement action that should be taken against foreign pharmaceutical manufacturers when GMP deficiencies are found. For 49 of the 230 foreign inspections reviewed during this period, field investigators concluded that the severity of the GMP deficiencies they observed warranted that CDER initiate official action against the manufacturers.

[12]FDA's field offices are responsible for determining the severity of inspection findings and enforcing facility compliance for U.S. pharmaceutical manufacturers. As a result, even in instances where CDER does not approve the enforcement actions recommended by the district offices, CDER does not downgrade the field offices' classifications of domestic inspections when violations are identified. Consequently, unlike foreign manufacturers, U.S. pharmaceutical manufacturers are subject to reinspections to verify that promised corrective actions have been implemented and manufacturing operations meet GMP requirements.

However, CDER officials downgraded the inspection classifications and recommendations for enforcement action in 32 of these inspections. CDER officials decided that rather than classify these inspections OAI, 32 of the 49 inspections (65 percent) should be classified VAI. CDER officials also upgraded the field investigators' classifications and recommendations for enforcement action for two foreign inspections and classified them OAI rather than VAI.

FDA officials believe that in some instances the agency can adequately verify that foreign manufacturers have corrected serious deficiencies without reinspecting them. They said that foreign pharmaceutical manufacturers nearly always respond in writing concerning corrective actions taken as a result of the observations listed on the FDA form 483. They said that these responses typically include copies of the manufacturer's documentation of the corrective actions taken, such as photographs, laboratory test results, and corrected manufacturing procedures. Consequently, FDA officials said they can evaluate a manufacturer's corrective actions to ensure the safety, purity, and quality of its pharmaceutical products without conducting a reinspection based on the deficiencies found, the documentation provided, and the manufacturer's history of implementing corrective action. While we recognize that there may be instances in which documentation could suffice to verify the correction of manufacturing deficiencies, inspections of facilities in China and India that we reviewed give instances in which such documentation may not have been sufficient.

A pre-approval inspection of a bulk drug manufacturer in India found several deficiencies in the procedures used to test impurity levels in the product being manufactured. Although ORA personnel recommended withholding approval of the new drug application until corrective actions had been implemented, CDER changed the final inspection classification based on its review of the manufacturer's written explanation of the actions it was taking to correct the deficiencies identified during the inspection. CDER did not request a reinspection to verify that the corrective actions had been taken, even though FDA documents raised questions about the trustworthiness of the manufacturer. According to these documents, FDA had been notified several years earlier that this manufacturer had informed the U.S. Department of Commerce that it was no longer making a particular pharmaceutical product, despite evidence that the manufacturer was still shipping the product to the United States.

In another case, FDA conducted a for-cause inspection of a bulk pharmaceutical manufacturer in India to investigate reports that the manufacturer was using chloroform in its manufacturing process (a substance that had been found at higher than acceptable levels in the bulk pharmaceutical chemical). While the investigators found that the manufacturer was no longer using chloroform, they identified other deficiencies in how the company was measuring the impurities present in other bulk drug products that an FDA chemist characterized as "incompetence bordering on fraud." The investigators recommended from these deficiencies that the manufacturer be considered an unacceptable source of bulk pharmaceutical chemicals. CDER disagreed with this recommendation after reviewing the manufacturer's response to the investigators' findings and accepted the manufacturer as a supplier of bulk pharmaceutical chemicals without verifying that it had corrected deficiencies in its impurity testing procedures.[13]

FDA Conducts Infrequent Routine Inspections of Foreign Pharmaceutical Manufacturers

FDA's 1988 and 1993 internal evaluations found that while FDA routinely conducted surveillance inspections of domestic pharmaceutical manufacturers, foreign manufacturers were typically inspected only when they were listed in new drug applications. The evaluations concluded that this practice, which FDA said was because of limited resources, was unreasonable and unfair to domestic manufacturers. In addition, FDA's 1993 evaluation concluded that in the absence of reinspections, FDA could not adequately verify that foreign manufacturers corrected deviations from GMPs that had been observed during prior FDA inspections. Both evaluations recommended that FDA increase the frequency of its inspections of foreign manufacturers that supply approved pharmaceutical products to the United States.

FDA has authority to inspect foreign pharmaceutical manufacturers exporting their products to the United States under the Food, Drug, and Cosmetic Act. The purpose of the foreign inspection program is to ensure that internationally manufactured pharmaceutical products meet the same GMP standards for quality, safety, and efficacy that are required of domestic manufacturers. However, FDA is not required to inspect foreign pharmaceutical manufacturing facilities every 2 years as it is required by statute to do for domestic pharmaceutical manufacturers that must be registered with the agency. Enforcing GMP compliance through routine surveillance inspections is FDA's most comprehensive program for

Statute defining inspection frequency

[13]Again, according to FDA, more recent reinspections of these manufacturers found that they had implemented promised corrections and were in compliance with U.S. GMPs.

monitoring the quality of marketed pharmaceutical products. FDA also uses routine surveillance inspections to verify that manufacturers have corrected all less-serious GMP deficiencies that were observed in prior FDA inspections. Each year, FDA classifies about 65 percent of its foreign pharmaceutical inspections as VAI, which means that deviations from GMPs were found but they were not serious enough to warrant FDA intervention to ensure that corrections were made. In such instances, manufacturers agree to voluntarily correct any manufacturing procedures that do not comply with U.S. GMPs.

FDA's foreign inspection program has been predominantly a pre-approval inspection program—that is, most inspections of foreign manufacturers occur only when they are listed in new drug applications, with no routine follow-up thereafter. We found that the majority of FDA's foreign inspections of pharmaceutical manufacturers were conducted to ensure that before a new drug application was approved, each manufacturer listed as a supplier of a bulk pharmaceutical chemical used in the manufacture of the finished pharmaceutical product had been inspected within the previous 2 years and found to comply with GMPs. During fiscal year 1995, about 80 percent of FDA's foreign inspections were of pharmaceutical manufacturers listed in new drug applications. The remaining 20 percent consisted of routine surveillance inspections of accepted foreign pharmaceutical manufacturers. Consequently, FDA had few opportunities to verify that foreign pharmaceutical manufacturers had implemented prescribed corrective actions in response to prior inspections where less-serious GMP deviations were observed and were producing pharmaceutical products in compliance with GMPs.

FDA officials could not tell us how often accepted foreign manufacturers are inspected. FDA has inspected about 1,100 pharmaceutical manufacturers since the foreign inspection program began in 1955. For each fiscal year from 1990 through 1996, FDA conducted about 100 routine surveillance inspections of accepted foreign pharmaceutical manufacturers annually. At this rate, assuming that resources for the program remain constant, FDA will inspect each accepted foreign pharmaceutical manufacturer only once every 11 years, provided it is not listed on a new drug application.

Of the 39 inspections we reviewed for pharmaceutical manufacturers in China and India from January 1, 1994, through May 15, 1996, 11 (28 percent) were routine inspections of manufacturers producing approved pharmaceutical products rather than inspections conducted as

part of FDA's review of new drug applications. On average, we found that approximately 4 to 5 years elapsed between routine inspections of manufacturers in China and India producing approved pharmaceutical products for the U.S. market, more than twice FDA's 2-year inspection requirement for domestic pharmaceutical manufacturers.

FDA Plans to Conduct More Routine Inspections of Foreign Pharmaceutical Manufacturers

In June 1997, FDA's foreign inspection working group proposed a strategy for scheduling more routine surveillance inspections of accepted foreign pharmaceutical manufacturers. Led by the Deputy Commissioner of Operations, the group was asked to review the program and identify areas for improvement. The working group found that serious deviations from GMPs were identified more often in foreign pre-approval inspections (42 percent), compared with 18 percent at U.S. manufacturers. They concluded that by relying primarily on pre-approval inspections, FDA did not provide the necessary assurance that imported pharmaceutical products were manufactured in compliance with GMPs. The foreign inspection working group proposed that FDA's foreign inspection program include more routine surveillance inspections and fewer pre-approval inspections. To accomplish this, they suggested that FDA conduct fewer pre-approval inspections of accepted foreign manufacturers. Instead, they recommended that FDA use information from routine surveillance inspections in approving new drug applications in which accepted foreign manufacturers are listed.

Recognizing that FDA does not have sufficient resources for frequent inspections of all foreign manufacturers of pharmaceutical products imported into the United States, the working group proposed using risk-based criteria to prioritize the foreign manufacturers that FDA inspects. FDA's four-tier surveillance inspection strategy would vary the frequency of routine surveillance inspections depending on the public health risk associated with an accepted foreign manufacturer of an approved pharmaceutical product. Foreign pharmaceutical manufacturers whose prior inspections found serious deviations from GMPs would be placed in tier 1 and inspected annually. Routine surveillance inspections of all other foreign pharmaceutical manufacturers would vary from 3 to 6 years. Foreign manufacturers of pharmaceutical products that pose higher public health risks, such as sterile pharmaceutical products, would be placed in tier 2 and inspected every 3 years. Foreign manufacturers producing 10 or more pharmaceutical products for the U.S. market and those producing nonsterile bulk ingredients used in sterile finished pharmaceutical products would be placed in tier 3 and inspected every 5

years. All other foreign pharmaceutical manufacturers would be placed in tier 4 and inspected every 6 years (see table 4). The working group estimated that when the strategy is fully implemented, 60 percent of FDA's foreign inspections will be routine surveillance inspections. The remaining 40 percent will be inspections of foreign pharmaceutical manufacturers listed in new drug applications.

Table 4: FDA's Four-Tier Strategy for Scheduling Surveillance Inspections of Accepted Foreign Pharmaceutical Manufacturers

Tier	Type of manufacturer	Number of firms[a]	Frequency of inspection
1	Foreign pharmaceutical manufacturers whose prior inspections were classified OAI	35	Every year
2	Foreign manufacturers producing sterile bulk, finished, and aerosol pharmaceutical products	154	Every 3 years
3	Foreign manufacturers producing 10 or more nonsterile bulk or finished pharmaceutical products; also, foreign manufacturers supplying 10 or more U.S. pharmaceutical manufacturers and foreign manufacturers producing nonsterile bulk ingredients used in sterile finished pharmaceuticals	484	Every 5 years
4	Foreign manufacturers producing fewer than 10 nonsterile bulk or finished pharmaceutical products	427	Every 6 years

[a]Represents the 1,100 pharmaceutical manufacturers FDA has inspected since the foreign inspection program began in 1955.

FDA began implementing its four-tier surveillance inspection strategy in fiscal year 1997 by including routine surveillance inspections within its pre-approval inspections. FDA reported that 151 of the 230 foreign pharmaceutical inspections conducted during fiscal year 1997 (66 percent) were classified pre-approval and routine surveillance inspections. In addition, FDA planned to conduct routine surveillance inspections of about 150 accepted foreign pharmaceutical manufacturers placed in tiers 1 and 2. This group includes manufacturers that produce sterile pharmaceutical products and manufacturers that had prior inspections that revealed serious deviations from GMPs. FDA reported, however, that it conducted only 60 inspections of these manufacturers. As a result, although FDA conducted more routine surveillance inspections, most foreign pharmaceutical inspections still are limited predominantly to

manufacturers listed in new drug applications rather than those considered high risk.

In developing its new four-tier surveillance inspection strategy, however, FDA did not include all foreign pharmaceutical manufacturers that it should consider for a routine surveillance inspection. According to FDA data, about 3,200 foreign manufacturers have submitted information to FDA listing the pharmaceutical products that they intend to export to the United States. However, FDA prioritized for routine surveillance inspections only the 1,100 foreign pharmaceutical manufacturers that it had previously inspected. Consequently, FDA's scheduling strategy does not account for almost two-thirds of the foreign manufacturers that may be exporting pharmaceutical products to the United States. Moreover, according to the FDA official in charge of developing the surveillance inspection strategy, FDA may never inspect the majority of foreign manufacturers placed in tiers 3 and 4. However, while FDA has recognized that it does not have sufficient resources to routinely inspect all foreign manufacturers of pharmaceutical products imported into the United States, its strategy does not ensure that every foreign manufacturer exporting pharmaceutical products to the United States complies with U.S. quality standards.

Serious Problems Persist in Managing Foreign Inspection Data

Although both FDA's 1988 and 1993 internal evaluations identified serious problems in its foreign inspection data systems, the agency still lacks a comprehensive, automated system for managing its foreign inspection program. Instead, the information FDA needs to identify the foreign pharmaceutical manufacturers it is responsible for inspecting, manage its foreign inspection workload, and monitor inspection results and enforcement actions is contained in 15 different computer systems, very few of which are integrated. As a result, essential foreign inspection information is not readily accessible to the different FDA units that are responsible for planning, conducting, and reviewing inspections and taking enforcement actions against foreign manufacturers. While FDA's working group recently proposed several actions that FDA officials hope will correct these data system problems, they have not been implemented.

Lack of Comprehensive Automated Information System Inhibits Effective Management of Foreign Inspection Data

FDA's 1988 internal evaluation found that its automated field management information system did not contain complete information for 37 percent of the foreign inspections that FDA conducted during fiscal years 1982 through 1987. Specifically, the Program Oriented Data System (PODS) did not contain the results of 673 of the 1,813 foreign inspections that FDA investigators had conducted during this period. Moreover, the system did not contain any data for 251 of these inspections (14 percent). The evaluation attributed the missing inspection results to PODS not being updated after CDER's review and classification of the inspection reports. The evaluation recommended that FDA revise its procedures for entering foreign inspection data in PODS.

FDA's 1993 internal evaluation found that essential data on foreign pharmaceutical manufacturers were not readily accessible to agency personnel. The evaluation indicated that comprehensive data for a foreign pharmaceutical manufacturer should include (1) its inspection history, (2) the results of its last FDA inspection, (3) the identification of responsible company personnel, (4) its U.S. agent or representative, (5) the products that it supplied to the United States, and (6) the domestic manufacturers and distributors that it supplied. The evaluation found that comprehensive foreign inspection information could be obtained only by searching multiple computerized databases and FDA headquarters' files. For example, the evaluation noted several instances in which ORA investigators conducting domestic inspections suspected that U.S. manufacturers had received adulterated bulk pharmaceutical chemicals from foreign manufacturers. However, the investigators' efforts to substantiate these suppositions were hampered because they could not readily gain access to comprehensive data for foreign pharmaceutical manufacturers. The evaluation recommended that FDA use its field management information system to provide agencywide access to complete data for all foreign manufacturers shipping pharmaceutical products to the United States.

In 1994, FDA began using a new information system to support the foreign inspection program. The Travel and Inspection Planning System (TRIPS) was specifically developed to assist FDA's foreign inspection planning staff in managing foreign inspection assignments and the program's budget. TRIPS is also used to monitor whether the inspection report has been completed as well as the results of the inspection. However, TRIPS is accessible to only ORA headquarters staff. As a result, foreign inspection data are not readily accessible to the different FDA units responsible for conducting foreign inspections and reviewing inspection results. FDA plans

to make data from TRIPS more broadly available within the agency when it upgrades its field management information system in fiscal year 1998.

TRIPS and PODS have not significantly improved the quality of FDA's foreign inspection data. Our analysis of data recorded in TRIPS and PODS disclosed that these systems did not contain the results of 111 of the 759 inspections (15 percent) FDA conducted of foreign pharmaceutical manufacturers between January 1, 1994, and May 15, 1996. For 68 of the 111 inspections, the database did not identify the foreign manufacturer that was inspected. TRIPS and PODS also did not include the correct inspection results for 10 of the 39 pharmaceutical manufacturers FDA inspected in China and India during this period. Specifically, the inspection results were missing for two of these manufacturers and were incorrect for eight others. The database errors in recording the results of inspections conducted in China and India occurred because the systems were not updated after CDER staff reviewed and classified the inspection reports. Without complete and accurate data, FDA cannot ensure that all "high-risk" foreign pharmaceutical manufacturers are targeted for more frequent routine surveillance inspections.

We also found that essential foreign inspection data are not readily accessible to the different FDA units responsible for planning and conducting domestic and foreign inspections, and conducting import operations. The information that FDA needs for identifying foreign pharmaceutical manufacturers, verifying their compliance with federal laws and regulations, and screening foreign-produced pharmaceutical products for importation is dispersed among 15 automated databases, most of which do not interface.

FDA's multiple and unlinked databases inhibit the effective management of the foreign inspection program by impeding the flow of foreign inspection data to agency personnel for use in screening foreign pharmaceutical products offered for entry into the United States. For example, table 5 illustrates how the lack of linkage between 8 of FDA's 15 databases not being linked impedes the flow of essential foreign inspection data. The first four databases described in the table are used by FDA's district offices to support import operations. The four other databases described in the table are used by FDA headquarters staff for monitoring foreign pharmaceutical manufacturers' compliance with federal statutes and regulations. However, because these systems do not interface, comprehensive data about foreign manufacturers are not readily available to FDA district personnel screening imported pharmaceutical products.

Consequently, much of the same data must be retrieved from one automated system to be manually entered into others. Moreover, staff must search multiple data systems to obtain a comprehensive profile of a foreign pharmaceutical manufacturer. FDA also cannot easily match foreign manufacturers that have listed with the agency with their compliance status and the pharmaceutical products that are imported into the United States.

Table 5: Limitations of Selected FDA Information Systems for Managing Foreign Manufacturers and Imported Pharmaceutical Products

System	Description	Limitation	Link to FACTS[a]
Compliance Status Information System (COMSTAT)	Provides the compliance status (acceptable or unacceptable) of foreign drug manufacturers based on the results of GMP inspections. These data are shared with other federal and state agencies and foreign countries to ensure that pharmaceutical products purchased or cleared for import meet applicable quality standards.	Does not interface with OASIS to automatically assist import officers in evaluating the compliance status of foreign manufacturers offering pharmaceutical products for import into the United States.	Replace
Electronic Entry Processing System (EEPS)/Operational and Administrative System for Import Support (OASIS)	Automates screening and identification of imported products and facilitates sampling and testing of foreign-produced pharmaceutical products by interfacing with the U.S. Customs Service automated data system to retrieve information.	FDA cannot automatically screen and identify imported pharmaceutical products because many pharmaceutical products are identified by a miscellaneous code in EEPS/OASIS. Also, EEPS/OASIS does not include the unique identification number FDA assigns to each foreign pharmaceutical manufacturer; consequently, there is no direct cross-reference between identifiers in EEPS/OASIS and any center systems.	Integrate
Import Detention System (IDS)	Provides information about the detention of imported products, permitting FDA to identify significant problem areas requiring FDA action.	IDS does not include the unique identification number FDA assigns to each foreign pharmaceutical manufacturer; consequently, FDA cannot easily identify foreign manufacturers and their pharmaceutical products.	IDS will be replaced by OASIS.
Program Oriented Data System (PODS)	Supports the management of the domestic pharmaceutical inspection program and contains limited information on foreign inspections, such as the resources expended by FDA's district offices to conduct foreign inspections.	Does not interface with OCFITS; accordingly, compliance status must be entered into both systems. Sometimes contains incorrect inspection classification because final data are forwarded from CDER for input.	Replace

(continued)

System	Description	Limitation	Link to FACTS[a]
Drug Registration and Listing System (DRLS)	Provides information on foreign pharmaceutical manufacturers based on the statutory requirement that they list the drug products they ship to the United States.	Does not interface with COMSTAT to ensure that foreign manufacturers listing their pharmaceutical products with FDA have been inspected and comply with GMPs. Because the system does not include the identification number FDA assigns to each manufacturer, FDA cannot easily match foreign manufacturers that have listed their pharmaceutical products with their compliance status. Does not interface with OASIS to assist import officers by automatically comparing foreign manufacturers and pharmaceutical products listed to products offered for importation.	Interface
Establishment Evaluation System (EES)	Tracks requests for and monitors the status of GMP inspections of pharmaceutical manufacturers named in new, abbreviated, and supplemental drug applications. Supports CDER's pre-approval inspection process by permitting electronic communication with field offices.	EES-entered information is not captured by COMSTAT.	Interface
Office of Compliance Foreign Inspection Tracking System (OCFITS)	Tracks the results of CDER's Office of Compliance reviews of foreign inspection reports and recommendations for FDA enforcement action.	Does not interface with COMSTAT, PODS, or TRIPS; consequently, some of the same information must be entered into all four systems.	None
Travel and Inspection Planning System (TRIPS)	Provides data on inspections of foreign pharmaceutical inspections, including the manufacturer, the drug products covered, time expended, and inspection results. Facilitates the scheduling of foreign travel and managing the foreign inspection travel budget.	Does not interface with COMSTAT, OCFITS, or PODS, thereby requiring much of the same data to be entered into each system.	Replace foreign firms/ inspection functions

[a]FACTS will completely or partially replace many functions now provided by FDA's field information system and other independent systems used by ORA headquarters and personnel in the field. Also, FACTS will support automated interfaces with several existing FDA systems. Some of these systems will receive information from FACTS, others will pass information to FACTS, and a few will do both. OASIS will be integrated with FACTS. Although OASIS and FACTS will be separate applications, they will share parts of the same database to manage information about manufacturers of FDA-regulated products and authorize user access to the system.

FDA's foreign inspection working group concluded in June 1997 that the agency continues to be plagued by having too many databases that do not automatically interface. FDA is relying on a new automated field management information system to provide agencywide accessibility to comprehensive foreign inspection data. The Field Accomplishments and Compliance Tracking System is expected to replace approximately 22 computerized databases and support automated interfaces with several

existing databases. The first installment of FACTS, which is to include an inventory of foreign and domestic pharmaceutical manufacturers, is scheduled to go on line during fiscal year 1998. FDA also plans to develop additional FACTS components to assist the agency in managing its foreign inspection workload and compliance activities. These components will be included in the second installment of FACTS, which is scheduled for fiscal year 1999.

Incomplete List of Foreign Manufacturers Shipping Drugs to the United States Hinders Inspection Planning

FDA's 1988 internal evaluation found that the agency did not maintain an inventory of all foreign pharmaceutical manufacturers that were subject to FDA regulation. At that time, the only computerized file of foreign manufacturers shipping pharmaceutical products to the United States was maintained on a personal computer that could be accessed only from within one FDA unit. The file listed the foreign pharmaceutical manufacturers that FDA had inspected and the results of the last inspection. The internal evaluation concluded that this file was inadequate because it did not contain an inspection history for each foreign pharmaceutical manufacturer that had advised FDA that it intended to ship pharmaceutical products to the United States. As a result, FDA could not ensure that it was aware of, and therefore inspecting, all foreign pharmaceutical manufacturers that were under its jurisdiction.

FDA's 1988 evaluation recommended that the agency develop a comprehensive inventory of all foreign manufacturers shipping pharmaceutical products to the United States that could be used to improve long-range inspection planning and scheduling. To use resources better and increase knowledge agencywide, the evaluation also recommended that this inventory be available on FDA's automated field information system.

FDA's 1993 internal evaluation found the same problem. According to the evaluation, the lack of an inventory of the foreign manufacturers that were shipping pharmaceutical products to the United States made it virtually impossible for FDA to inspect foreign manufacturers as frequently as domestic pharmaceutical manufacturers. The evaluation detailed several instances in which a database with a comprehensive history of each establishment's previous inspections would have assisted in identifying problems in foreign pharmaceutical manufacturers. FDA's 1993 evaluation recommended that the agency use its automated field information system to develop an accurate and comprehensive inventory of all foreign manufacturers shipping pharmaceutical products to the United States.

It remains difficult for FDA to determine the number of foreign manufacturers shipping pharmaceutical products to the United States that should be considered for periodic inspections. Recently, an FDA official told us that the agency had to search four data systems just to determine the number of foreign manufacturers that should be considered for routine postapproval surveillance inspections.[14] They found that the systems did not include a common data element to permit them to easily identify a foreign manufacturer from system to system. Because the names and addresses of foreign manufacturers are sometimes incomplete or inaccurate, FDA officials found that matching data among the systems was an arduous, manual, and inconclusive effort.

The June 1997 report by FDA's foreign inspection working group acknowledged that the agency still lacked a complete list of foreign manufacturers that were shipping pharmaceutical products to the United States. According to the report, about 3,200 foreign pharmaceutical firms were listed with FDA as indicating their intent to ship products to the United States. However, FDA internal databases indicated that only about 1,100 pharmaceutical firms had been inspected by the agency. FDA officials could not explain why the remaining 2,100 firms had not been inspected.

The foreign inspection working group proposed two options for developing an official inventory of all foreign manufacturers that ship pharmaceutical products to the United States. One option would be for FDA to seek authority to require foreign pharmaceutical manufacturers to register and update their registration information annually. The other would use data from existing information systems to develop an official establishment inventory of foreign pharmaceutical manufacturers.

FDA's efforts to reconcile data from several of its databases to more accurately estimate the number of manufacturers that it should consider for inspection under its four-tier inspection strategy should identify all foreign manufacturers that are shipping pharmaceutical products to the United States. When completed by April 1998, FDA should have a comprehensive inventory of all foreign manufacturers shipping pharmaceutical products to the United States. This information could then be used to improve FDA's planning and scheduling of foreign pharmaceutical inspections.

[14]The systems were the Compliance Status Information System, the Drug Registration and Listing System, and the Travel and Inspection Planning System. (These systems and their functions are described in table 5.) The fourth system was the Drug Master File Information System that is used to track the receipt of submissions to the agency and may include foreign drug manufacturing processes.

Conclusions

Since 1955, FDA has inspected foreign pharmaceutical manufacturing facilities to ensure that drug products exported to the United States meet the same standards of safety, purity, and quality required of domestic manufacturers. However, two internal FDA evaluations in the past 10 years identified serious problems with the foreign inspection program that raised questions about FDA's ability to ensure that American consumers are protected from contaminated or adulterated drug products. FDA has taken some action to address these problems. However, we found indications that certain aspects of the foreign inspection program still need improvement.

FDA continues to experience problems in ensuring that inspection reports are submitted in a timely manner and that necessary enforcement actions are promptly initiated to prevent contaminated and adulterated pharmaceutical products from entering the United States. In addition, when FDA headquarters downgrades the severity of the inspection classifications recommended by field investigators, FDA is not verifying corrective actions that foreign manufacturers have promised to take to resolve serious manufacturing deficiencies. This impairs FDA's ability to ensure that American consumers are protected from potentially serious health risks posed by adulterated drug products.

FDA's risk-based inspection strategy recognizes that the agency does not have sufficient resources to routinely inspect all foreign manufacturers of pharmaceutical products imported into the United States. However, even though the strategy is intended to direct inspection resources according to risk, FDA's foreign inspection program continues to be driven by new drug applications and the agency acknowledges that it may never inspect most foreign manufacturers exporting pharmaceutical products to the United States.

Recommendations to the Commissioner of the Food and Drug Administration

To improve the effectiveness of FDA's foreign inspection program to ensure that only safe, pure, and high quality drugs are imported into the United States, we recommend that the Commissioner of FDA

- ensure that serious manufacturing deficiencies are promptly identified and enforcement actions are initiated by requiring investigators to prepare inspection reports and CDER to issue warning letters within established time periods and
- reexamine and revise FDA's foreign inspection strategy to provide adequate assurance that all foreign manufacturers exporting approved

pharmaceutical products to the United States comply with U.S. standards. At a minimum, the strategy should include (1) timely follow-up inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies and that promised to take corrective action and (2) periodic surveillance inspections of all foreign pharmaceutical manufacturers, not just high-risk manufacturers.

Agency Comments and Our Response

In commenting on a draft of this report, FDA took issue with a number of our findings and recommendations. As discussed earlier, FDA believes it has made substantial improvement in the timeliness of inspection reports and enforcement actions. While we recognize FDA's progress, we note that the agency is still falling short of its standards for timeliness. As a result, we believe that FDA needs to monitor its investigators and CDER to ensure that they comply with established time periods in preparing inspection reports and issuing warning letters.

FDA was critical of our draft on several counts. FDA said we had accepted the recommendations in the 1993 discussion paper without verifying their validity or feasibility. FDA claimed that the findings and recommendations in the 1993 discussion paper were flawed in significant ways that limited its usefulness to the agency. We note, however, that subsequent to the discussion paper, in a 1995 memorandum to the agency's Assistant Inspector General, FDA officials reported that they had thoroughly reviewed the discussion paper, investigated the issues raised, verified program weaknesses, and had either begun or agreed to implement 10 of the 13 recommendations contained in the discussion paper.[15]

FDA also took issue with how our report described the processes followed by its district and headquarters for classifying domestic and foreign inspection reports. Specifically, FDA stated that the review performed by the supervisor or team leader in the district office is not considered to be a district endorsement of the investigator's recommendation. However, our review of FDA documents that describe the process for classifying domestic and foreign inspection reports supports our characterization. FDA issued guidance to its district offices in September 1996 indicating that beginning in fiscal year 1997, before inspection reports are forwarded to CDER, they "will be reviewed and endorsed by district management consistent with local procedures and timeframes for domestic reports." Also, in its memorandum to the Assistant Inspector General, FDA officials

[15]Memorandum from Associate Commissioner for Management, FDA, to Assistant Inspector General for Public Health Service Audits, Office of the Inspector General, Department of Health and Human Services, April 20, 1995.

reported that district offices had began endorsing foreign drug inspection reports before the 1993 discussion paper was issued.

FDA did not concur with our recommendation for conducting more frequent inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies and have promised to take corrective action. FDA incorrectly suggests that our recommendation was based on the premise that a final classification that is lower than the recommended classification is always wrong if it results in a less-serious classification. Rather, our report questions FDA's ability to verify the adequacy of some corrective actions that foreign manufacturers promised to take to resolve serious manufacturing deficiencies without reinspecting them.

FDA also did not concur with our recommendation regarding the implementation of its routine surveillance inspection strategy. Given further clarification of the strategy, we have modified our recommendation.

FDA's written comments on a draft of this report are reproduced in appendix I. FDA also provided technical comments, which we considered and incorporated where appropriate.

As we arranged with your office, unless you publicly announce the report's contents earlier, we plan no further distribution until 30 days after its issue date. We will then send copies of this report to the Secretary of Health and Human Services, the Commissioner of the Food and Drug Administration, the Director of the Office of Management and Budget, and others who are interested. We will also make the report available to others upon request.

Please contact me on (202) 512-7119 or John Hansen, Assistant Director, on (202) 512-7105, if you or your staff have any questions. Others who contributed to this report are Gloria E. Taylor, Brenda R. James, and David Bieritz.

Sincerely yours,

Bernice Steinhardt

Bernice Steinhardt
Director, Health Services Quality
and Public Health Issues

Contents

Abbreviations

CDER	Center for Drug Evaluation and Research
FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration
GMP	good manufacturing practice
NAI	no action indicated
OAI	official action indicated
ORA	Office of Regulatory Affairs
PODS	Program Oriented Data System
TRIPS	Travel and Inspection Planning System
VAI	voluntary action indicated

Appendix I

Comments From the Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 14 1997

Ms. Bernice Steinhardt
Director, HEHS
U.S. General Accounting Office
Room 5A26
441 G Street, N.W.
Washington, D.C. 20548

Dear Ms. Steinhardt:

Enclosed are the Food and Drug Administration's comments on the GAO Draft Report entitled "Food and Drug Administration: Improvements Needed In the Foreign Drug Inspection Program," GAO/HEHS-98-21, October 1997.

Sincerely,

for Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure

COMMENTS OF THE FOOD AND DRUG ADMINISTRATION ON THE GENERAL ACCOUNTING OFFICE DRAFT REPORT ENTITLED, FOOD AND DRUG ADMINISTRATION: Improvements Needed In The Foreign Drug Inspection Program GAO/HEHS-98-21

GENERAL

We appreciate the opportunity to review the draft report and offer the Food and Drug Administration's (FDA or the Agency) comments. We recognize that both the General Accounting Office (GAO) and FDA have put a great deal of effort into this study, and we are happy to assist the GAO evaluators to ensure that the final report is accurate. In our review of the draft report, we found a number of areas where there are apparently misconceptions and some errors of fact that need to be corrected.

Over the last few years, as more drugs, particularly bulk drugs, are being imported from many different countries, FDA has made significant changes to the foreign inspection program by increasing the number of foreign drug inspections, increasing the length of time spent on the inspections, and by expanding the inspections to include more aspects of the Current Good Manufacturing Practices (CGMP) than was done before.

In addition, approximately two years ago, FDA's Deputy Commissioner for Operations established a working group to analyze the current foreign inspection and import programs, describe their current operations, and make recommendations for improving the programs within existing resources. The working group consisted of representatives of each of FDA's five Centers and the Office of the Commissioner. In May of 1997, the working group submitted a risk-based plan to the Deputy Commissioner that, if implemented, would provide a solid basis for making decisions about the approvability of new products as well as the admissibility of products presented at U. S. ports for entry. The plan also calls for focusing Agency resources on the high-risk product manufacturers to ensure that they either comply with CGMPs or are cease marketing products in the U. S. The plan was adopted by the Agency, and currently is being implemented to allow FDA to leverage its scarce resources to assure that the nation's drug supply is safe.

1993 DISCUSSION PAPER

The draft report reflects a misunderstanding of the 1993 "internal review" of the foreign drug inspection program. As we stated in the exit conference on November 5, the 1993 document is, in fact, an internal discussion paper entitled, "Recommendations to Strengthen Surveillance and Enforcement Operations Associated with the Importation of Human Drugs" which was written by a Regional Food and Drug Director. The recommendations were formulated on the basis of data from one Region only, and did not include Office of Regulatory Affairs (ORA) headquarters or CDER input. While the 1993 discussion paper was thoroughly reviewed, the issues investigated,

and the verified program weaknesses addressed, it should not be weighted equally with the Agency evaluations done in 1988 and 1997. This is especially important as the 1993 discussion paper served as the springboard for the current GAO evaluation, and the evaluators accepted the recommendations in the discussion paper without independently verifying their validity/feasibility. FDA's review of the 1993 discussion paper found it to be flawed in significant ways that limited its usefulness to the Agency. The evaluators were given a copy of FDA's memorandum to the Assistant Inspector General for Public Health Service Audits, OIG, in which many of the findings in the 1993 discussion paper were rebutted by FDA. Therefore, many of its recommendations have not been implemented, nor are there plans to do so. Those recommendations found to be valid and feasible were adopted.

CLASSIFICATION AND PROCESS

The draft report implies that there may be a significant difference between the processes followed by FDA's districts and headquarters for classifying domestic and foreign Establishment Inspection Reports (EIR). The draft report also frequently uses the terms "disagreed with" and "downgraded" to describe an apparent difference between domestic and foreign drug inspection processes (pages 25-31 and Footnote 8). In fact, the processes followed by both the Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) are very similar. In both cases, an investigator recommends, on the basis of his/her knowledge about the manufacturer's operations as of the time of the inspection, an Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or a No Action Indicated (NAI) classification of an inspection report. For a domestic OAI classification, the investigator recommends a classification and forwards the EIR package to the Investigations Branch Supervisor or Team Leader, who either agrees with the recommended classification or disagrees and adjusts the classification accordingly. Domestic EIRs and supporting documentation are then forwarded to the District Compliance Branch which may agree with the classification (endorse it), or disagree with the classification and change it to a different classification.

For most foreign inspections, an investigator prepares the EIR and recommended classification (OAI, VAI, NAI) just as for domestic inspections. The EIR may be reviewed by the Supervisor or Team Leader. This review is not considered to be a District endorsement of the inspector's recommendation. There is no further District involvement from this point. The EIR is forwarded to CDER, Office of Compliance, Foreign Inspection Team (FIT), for evaluation and classification. Final classifications by CDER are based upon the inspection report as well as FIT's knowledge of current policies, regulations, practices and the public health significance of any violations.

The EIR classification is the point at which the inspections and compliance are merged to evaluate and determine the compliance status of a firm. The compliance function supports the inspection functions and complements it with expertise regarding the Federal Food, Drug, and Cosmetic Act (FFDCA), FDA policies and procedures, the documentation supplied by the manufacturer in

response to the 483, their compliance history, and any further processing the imported drug may undergo, similar situations at other firms and how they were classified, how similar cases have been adjudicated, and the public health significance of the violations. This process is transparent and rapid in the districts. The purpose of the classification is to help the Agency determine what, if any, regulatory action should be initiated to correct a violation. While not all violative conditions require an immediate reinspection of the manufacturer, during the next inspection, whenever it may be, FDA always confirms that the corrections were made. This procedure helps direct the use of FDA's limited resources to those cases where it is important to assure correction of the most serious deficiencies by an immediate reinspection and where a routine inspection will suffice to protect the public.

In addition, the draft report indicates that CDER and the field investigators often disagree on the classification of inspection findings and the severity of the enforcement action. There is no evidence that inspectors disagree with final CDER classification once it has been made. The only thing established is that CDER did not accept the recommendation. The report does not attempt to assess the validity of CDER action, which is based on all the facts, or whether the inspector would agree if he/she had all the facts available to CDER. In both foreign and domestic inspections, final classification represents the most well-thought-out decision based on the current inspection, past history of the establishment, and the significance of the drug. It is not valid or prudent to assume that the assignment of a final classification by CDER that is lower than the initial recommended classification will result in violative products entering the U.S.

Finally, the report states that, "FDA officials have acknowledged that because of resource limitations, they sometimes downgrade inspection classifications and approve new drug applications based on foreign manufacturers promises to implement corrective actions." As FDA explained during the exit conference, changing inspection classifications is not done to conserve resources. Rather, any change in classification by CDER is based solidly on the information contained in the EIR and other relevant other information that bears on the actions FDA would initiate to correct a violative condition.

GAO RECOMMENDATION

"To improve the effectiveness of FDA's foreign inspection program to ensure that only safe, pure and high quality drugs are imported into the United States, we recommend that the Commissioner of FDA:

-- ensure that serious manufacturing deficiencies are identified and enforcement actions are initiated, by requiring investigators and CDER to prepare inspection reports and issue warning letters within established time frames;"

FDA COMMENT

FDA acknowledges that there are unique difficulties in completing foreign inspection reports on a timely basis. FDA has made changes in the length of scheduled foreign inspection trips, provided for report writing days during the foreign trip, and emphasized to district management that foreign travelers must be able to complete foreign inspection reports before being assigned other duties. Field Management Directive #86, Revised 7/31/96, identifies time frames for completion of foreign drug EIRs. Additionally, this topic was included in the most recent foreign inspection manual and the introduction to the foreign inspection training course held in May, 1997. Also, foreign inspection reports are now sent directly to CDER, Foreign Inspection Team, upon completion to eliminate a previous ORA step in the process.

FDA believes that the changes made and regular emphasis by FDA management is improving the timeliness of EIRs and decision-making. Table D shows the EIR submission data for FY-97 and Table E shows the processing times for Warning Letters issued. The results shown in both tables are based on CDER's review of 257 inspection reports as of November 7, 1997 of which 230 involved inspections of manufacturers.

TABLE D

Number of Work Days from Completion of FY-97 Foreign Inspections to Submission of Inspection Reports to CDER's Office of Compliance (Based on Initial EIR Classifications by Districts)

Submitted to CDER (in work days)	Official Action Indicated	Voluntary Action Indicated	Total Number of Inspection EIRs Reviewed Within Specified Time Frame	Percent
30 Days or Less	28	47	75	46.9
31 - 60 Days	17	44	61	38.1
61 - 90 Days	4	17	21	13.1
91 - 120 Days	0	2	2	1.3
121 Days or More	0	1	1	0.6
Total	49	111	160	100

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Table D shows that 47% of FY97 OAI/VAI EIRs were submitted to CDER in 30 days or less and 38% were submitted in 31-60 days. The average time for submission of OAI and VAI reports for FY-97 is 34 days and 41 days, respectively

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TABLE E

Number of Work Days from Receipt of FY-97 Foreign Inspection EIRs to Issuance of Warning Letters

Time Frame (In Work Days)	Number of Warning Letters Issued	Percent
15 Days or less	3	30
16 - 30 days	4	40
31 - 45 days	2	20
46 - 60 days	1	10
61 - 75 days	0	0
76 - 90 days	0	0
91 - 105 days	0	0
106 or more days	0	0
Total	10	100

Table E shows that 30% of FY-97 Warning Letters were issued in 15 days or less after CDER received the EIRs, and another 60% were issued within 45 days. The average time for processing FY-97 Warning Letters is 24 days. For FY-96, CDER data showed that 26% of the Warning Letters issued in 15 days or less, and another 53% issued within 45 days after receipt of the EIR. The average time for processing FY-96 Warning Letters was 41 days.

To conclude, CDER analysis of FY-97 data shows a modest improvement in the submission times for OAI/VAI inspection reports, and a substantial improvement in the time expended by CDER in processing Warning Letters. The average processing time has been reduced from 41 days to 24 days; or a reduction of 42%.

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GAO RECOMMENDATION

-- "revise the risk-based inspection strategy to conduct more frequent inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies; and"

FDA COMMENT

We do not concur. GAO may be basing this recommendation on the assumption that where inspection reports receiving a final classification of VAI after an initial recommendation of OAI, the OAI classification was, in fact, the correct assessment. In the absence of a re-review of final classifications, which GAO did not conduct, this would be an incorrect assumption. The Center-based compliance function is a separate, albeit complementary, function to the field-based inspection function. It cannot be assumed that a final classification which differs from the recommended classification is always wrong if it results in a less serious classification.

GAO RECOMMENDATION

-- "reevaluate plans for increasing the frequency of routine surveillance inspections of foreign pharmaceutical manufacturers to ensure that adequate resources are available to implement this strategy without diminishing FDA's ability to conduct pre-approval inspections."

FDA COMMENT

We do not concur. Rather than re-evaluating the plan at this time, FDA believes that it is more important to continue implementation of the plan and re-evaluate it in the future. FDA is committed to maximizing the use of routine surveillance inspections within existing resources. The FY97 results shown in Tables D and E, above, which are based on a review of 230 inspections of manufacturers show that 60 (26%) of the foreign drug inspections done during FY97 were classified as "post-approval" or surveillance inspections and 151 (65.7%) were classified as "pre-approval/CGMP" inspections. The strategy of including CGMP inspections as a part of pre-approval inspections is moving the program toward more uniform and balanced inspection coverage.

FDA also will analyze data from its newly installed OASIS program for processing import entries to determine which foreign drug manufacturers actually have products come into the U.S. Any foreign manufacturers that have not been inspected will be added to FDA's official inventory and scheduled for inspection based upon criteria in the new strategy.

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Exhibit 7

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Petition to Request the Food and Drug Administration to Rank Foreign and Domestic Drug Manufacturing Firms Together for Purposes of the Agency's Risk-Based Approach to Inspections and Take Other Steps to Reduce the Public Health Risks Associated with Imported Drugs	)	Docket No. _____

CITIZEN PETITION

The Synthetic Organic Chemical Manufacturers Association's (SOCMA's) Bulk Pharmaceuticals Task Force (BPTF) submits this petition to request that the Food and Drug Administration (FDA) take specific actions designed to allow it to better manage the risks to public health associated with the use of drugs manufactured or processed at foreign facilities.

The BPTF is an association for manufacturers of active pharmaceutical ingredients (APIs), excipients, and intermediates. The BPTF's primary objective is to seek clarification of current regulatory requirements and to interact with governmental agencies on emerging issues that may impact SOCMA members. SOCMA is the leading trade association of the specialty batch and custom manufacturing chemical industry, representing 300 member companies with more than 2000 manufacturing sites and over 100,000 employees.

I. ACTION REQUESTED

The BPTF respectfully submits this petition to request the Commissioner of Food and Drugs to allocate its resources to reduce the public health risk that imported drug products pose by:

1. ranking foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections;
2. listing "foreign facility" as a significant risk factor for purposes of its risk-based approach; and
3. implementing a program of monitoring the impurity profiles of imported over-the-counter (OTC) drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP), so that FDA may refuse entry under 21 U.S.C. § 381(a) to products that appear adulterated.

II. STATEMENT OF GROUNDS

A. Background

Domestic and foreign establishments importing drugs must register their establishment and list all drugs in commercial distribution.[1] A review of establishment registrations and drug lists reveal several important trends in drug manufacturing. In 2004, 2700 foreign drug manufacturing establishments were registered with the FDA versus 3300 domestic sites (excluding the 4500 domestic sites registered solely for the production of medical gases).[2] China and India led in the number of FDA registered facilities with 440 and 300 sites, respectively.[3] Approximately 51% of the registered foreign sites are API manufacturing facilities; the remaining are other establishment types, such as finished dosage plants and control laboratories.[4]

The number of finished drug products manufactured abroad for the U.S. market is increasing, accounting for four of ten prescriptions drugs now sold in this country.[5] A review of the FDA Type II DMF database also reflects the trend toward increasing foreign drug manufacturing: 87 percent of the 510 DMFs filed with the FDA in fiscal year 2004 were for products/APIs manufactured outside of United States.[6] Even if not all of these DMFs have yet been cross-referenced into approved applications, the numbers suggest that a greater proportion of drugs are likely to come from foreign countries in the future.

FDA is responsible for ensuring that all domestic and imported drug products are safe, effective, and in compliance with current good manufacturing practices (cGMPs).[7] It is cGMP that provides the assurance that each pill we consume has the same identity and strength and the same quality and purity characteristics as the product approved by FDA. FDA is required to inspect registered domestic establishments in any state every two years.[8] NDA/ANDA pre-approval inspections are conducted for specific new products, but domestic facilities also receive periodic, unannounced inspections for cGMP compliance. Based on CDER inspection statistics of 1999-2003 (Table I below), and the estimated number of domestic manufacturing sites registered, it

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[1] *See* Federal Food, Drug and Cosmetic Act (FDCA) § 510, 21 C.F.R. § 207.20, 21 C.F.R. § 207.20.

[2] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005.

[3] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[4] *See id.*

[5] *See* GOVERNMENT EXECUTIVE *at* http://www.govexec.com/dailyfed/1204/121404cdpm1.htm (*last visited* October 20, 2005). The proportion of APIs that are imported is even higher; at least 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported. *See* GAO/HEHS-98-21: General Accounting Office, GAO, Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives, Food And Drug Administration, *Improvements Needed in the Foreign Drug Inspection Program* (March 1998) [hereinafter 1998 GAO report].

[6] www.fda.gov/cder/dmf/index.htm

[7] *See* FDCA § 501(a)(2)(B).

[8] *See* FDCA § 510 (h).

appears that FDA is reasonably close in meeting the biennial inspections mandated of the domestic facilities.

Table I
CDER Manufacturing Plant Inspections

Fiscal Year	Domestic Inspections		Foreign Inspections
	NDA/ANDA	cGMP	
1999	2548	1844	220
2000	2229	1436	248
2001	2090	1497	249
2002	2166	1519	210
2003	1453	1512	184
2004	1375	1825	184

Source: CDER Reports to the Nation (for years 1999 to 2004)

FDA is not required to inspect foreign facilities every two years for the simple reason that FDA has no authority to enter a facility in a sovereign country unless invited. As partial compensation for FDA's lack of authority to inspect foreign facilities, the statute invites FDA to enter into cooperative arrangements with foreign officials to determine whether drug(s) should be refused admission into the United States.[9] Nonetheless, FDA is falling short of meeting its responsibility to safeguard the public from adulterated or misbranded drugs manufactured or processed at foreign facilities. Even though as much as 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported,[10] the Agency inspects foreign API suppliers and foreign suppliers of drug products for OTC applications infrequently, if at all. Indeed, inspections of foreign pharmaceutical manufacturers occur with far less frequency than the two-year interval Congress deems necessary for domestic manufacturers.

In fact, at the current rate of inspection, a foreign manufacturer is unlikely to be inspected for cGMP compliance at all, unless the firm is listed in an ANDA/NDA. In October 2000, Jane M Henney, M.D. testified before the Subcommittee on Oversight and Investigation that based on the Establishment Evaluation System database, 242 foreign API manufacturers, in 36 countries, appeared to have exported products into the U.S. in 1999, without having been inspected by FDA.[11] Forty-six of these firms were located in China and Hong Kong and eleven in India; according to 2004 data, firms in these countries now account for 49% of the drugs consumed in the U.S. It is worthy to note that the final rule requiring registration of foreign establishments did not take effect until February 11, 2002; therefore, the actual number of foreign facilities not inspected by the FDA may have been substantially higher than 242.

According to FDA's Center for Drug Evaluation and Research (CDER) Office of Compliance, 90 percent of the international drug inspections of facilities were limited to "pre-approval"

[9] *See* FDCA § 510 (i).

[10] *See* 1998 GAO report, *supra* note 5.

[11] Jane M. Henney, M.D., Testimony to Chairman Fred Upton, Subcommittee on Oversight and Investigations, House of Representatives, October 3, 2000.

inspections, with the remainder being cGMP compliance or post-approval surveillance.[12] Thus, a majority of the foreign drug manufacturing sites were not inspected for cGMP compliance at all, and those that were inspected had little or no follow-up on the corrective action implemented in response to previous inspections.

In China and India, for example, more than five years may elapse between FDA inspections of a drug manufacturer. Moreover, FDA is still experiencing delays in taking enforcement action against foreign pharmaceutical manufacturers. In one case, FDA allowed a manufacturer in India to continue exporting its products to the United States despite an investigator's finding that the manufacturer could not adequately test for impurities in its product and water system; nearly two years passed before FDA determined that enforcement action had never been taken against this manufacturer.[13]

Statistics also show the number of Form 483s issued to foreign firms after an inspection is significantly higher in percentage than are issued to domestic firms[14] and serious deviations from GMPs were identified more often in foreign than U.S. pre-approval inspections.[15] If there had been enough cGMP inspections of foreign firms to generate comparable statistics, it is reasonable to assume that the higher violation rate for foreign facilities would be repeated.

Foreign facilities, in general, pose a greater risk to public safety because when a facility is inspected infrequently, as is the case for foreign manufacturers, there is a natural tendency for management to become complacent that what was adequate at the last inspection is still adequate. In the absence of a credible threat of reasonably frequent inspections, the "c" in cGMP gets lost. Maintaining cGMP compliance requires constant effort and vigilance. Minor deviations may not cause any apparent lack of quality, but it is a well-paved road from minor deviations to serious quality failures. Each step away from cGMP compliance appears to be a short term cost savings. Without creditable regulatory oversight, profits can displace the assurance of cGMP. Furthermore, the consequences for a foreign firm that fails an FDA inspection is loss of the US market; however, if a foreign firm complies with local laws, it may continue to operate and produce for its own domestic, and many other, markets. This, of course, is not the situation for U.S. drug manufacturers, which risk a much greater penalty for failing FDA inspections.

B. Risk-Based Inspection Ranking

FDA has stated that as part of its cGMPs for the 21st Century Initiative, it will pilot a risk-based inspection model for prioritizing drug manufacturing establishments for routine inspection.[16] We

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[12] Charles M. Edwards, *FDA International Inspections*, 27th International cGMP Conference, Univ. of Georgia, March 2003.

[13] *See* 1998 GAO report, *supra* note 5.

[14] *See id.*; *see also* Philip S. Campbell, *2004 Inspection Records & Compliance Issues*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[15] *See* 1998 GAO report, *supra* note 5.

[16] *See* FDA's *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model* (September, 2004), *available at* http://www.fda.gov/cder/gmp/gmp2004/risk_based.pdf.

understand that as part of this initiative, the Agency has started using a computer program to select manufacturers for inspection, which ranks domestic facilities, using risk factors such as specific product, processes used, recalls, violation history, and contamination potential.[17] We also understand that the agency will use this program for foreign manufacturers in 2006, but will rank domestic and foreign facilities separately.[18] In this regard, we urge FDA to risk-rank domestic and foreign facilities together. Additionally, we request that, based on the considerations noted above, the Agency specifically list "foreign facility" as a significant risk factor for purposes of its risk-based approach to inspections. Such action will assure that resources are actually allocated consistent with the risk, and thereby reduce the likelihood that quality problems associated with drugs would lead to injury, and even death, as happened in 1998-1999, when seventeen patients who were treated with gentamicin sulfate died – the common denominator linked to the deaths was the API of the drug originated from a Chinese supplier with varying levels of endotoxin and notable chemical impurities.[19]

One difficulty that may be perceived with risk ranking foreign and domestic firms together, however, is FDA's lack of authority to demand access to foreign facilities. In theory, this lack of authority could undermine the unified rankings because FDA would have to skip over facilities to which it could not gain access. In our opinion, this problem is more theoretical than real, at least in the case of facilities that are named in approved New Drug Applications. Foreign facilities that supply NDA holders typically establish Drug Master Files (DMFs) that describe the portions of the chemistry, manufacturing, and control operations associated with new drug production performed at the site. Because information provided in a DMF is incorporated by reference into the customer's New Drug Application, if a supplier were to deny access to FDA, for example to check records, the customer's NDA would be in jeopardy. As a result, the relationship between supplier and NDA holder (customer) gives FDA leverage over the suppliers—leverage that can be used to gain access to foreign suppliers.

C. Impurity Monitoring as a Surrogate for cGMP Inspections

A different approach, however, is required for foreign establishments that supply products other than those subject to a NDA. Most over-the-counter (OTC) drugs are not the subject of NDAs and ANDAs; rather, they are marketed pursuant to regulations referred to as "monographs" or an enforcement policy pending adoption of a final monograph.[20] Because there are no regulatory pre-approval barriers to entry for these products, formulators are free to source raw materials from any manufacturer and may change suppliers freely and frequently to obtain the lowest cost of goods. Quality assurance is a good investment only if there is a higher price to pay for poor

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[17] *See* presentation by Alicia Mozzachio, FDA inspector, *APIs and the Foreign Inspection Program*, at SOCMA's cGMP Compliance Conference for Pharmaceutical Ingredient Suppliers, Oct., 6, 2005; *see also* Pat Phibbs, *U.S., Foreign Firms Ranked Separately in Tool FDA Uses to Target Inspections*, Daily Report for Executives, Oct. 11, 2005.

[18] *See id.*

[19] A review of all the evidence indicated it was unlikely that endotoxin alone was responsible, but that it might have acted synergistically with a non-endotoxin pyrogen. *See* James F. Cooper, LAL TIMES, *Pyrogenic Reactions to IV Gentamicin*, December 1999; *see also* Steve Sternberg, USA TODAY, *FDA Probe Into Antibiotic Deaths Called Inadequate*, May 11, 2000.

[20] 21 C.F.R. Part 330.

quality. In the absence of effective oversight, quality assurance investments become unnecessary and unrecoverable costs. As long as the only production of imported mongraphed products (or ingredients) that are offered for import to the U.S meet the applicable specification requirements of the U.S. Pharmacopeia, there is virtually no incentive for such manufacturers to even implement GMP, let alone invest the time and attention required to stay up to date with cGMP.[21]

Indeed, if an OTC product or its components are manufactured in a foreign facility, the risk factors discussed above with respect to foreign suppliers to NDA/ANDA holders are further amplified. At this time, use of unproven or hazardous excipients in the formulations is possible because there currently is no systematic mechanism for detection or prevention of their use in such products. Additionally, just because adverse events are not associated with an OTC, does not mean there are no additional risks associated with foreign sites. Adverse events are difficult to correlate to an actual source or problem, especially considering that many OTC manufacturers may use numerous different suppliers over time for the same product with the same API and adverse effects of poor quality OTCs could take considerable time to appear.

Since cGMP non-compliance can be inferred by observing inconsistent impurity profiles in different batches of products, we ask that FDA implement a program to monitor the impurity profiles of imported OTC drugs for patterns that create the appearance of underlying cGMP violations. We recommend that FDA coordinate the priorities for this program based on the risk ranking of the facility that produces the product.

D. Conclusion

While the FY 2006 budget was signed into law on November 10, 2005,[22] we understand that the 2006 budget with regard to the foreign inspection programs is still unclear but, based on the proposed 2006 budget,[23] likely includes cuts to nearly all FDA's inspection programs, potentially reducing the foreign drug establishment inspection program by 5.8%. We sympathize with FDA's limitations in resources, but believe that if the agency is to fulfill its mandate to protect US consumers, it is imperative that the foreign manufacturing facilities responsible for exporting 80% of the bulk APIs into U.S. be inspected, at a minimum, to the same extent as domestic facilities. As Bernard Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner of FDA in 2001 stated, "FDA must improve foreign inspection and physical inspection coverage and oversight of foreign producers to be able to maintain the safety of products on that [sic] market that we believe Americans expect and demand."[24]

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[21] Although it is common for drug product manufacturers in the U.S. to qualify their suppliers, there is no explicit regulatory requirement for such inspections. *Cf.*, 21 C.F.R. Part 211.

[22] *See:* PL 109-97 http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=109_cong_public_laws&docid=f:publ097.109.pdf

[23] Julie Appleby, USA TODAY, *Budget Cuts FDA Safety Checks*, Feb.14, 2005.

[24] Bernard Schwetz, D.V.M., Ph.D, Acting Principal Deputy Commissioner, FDA, Testimony before the U.S. House of Representatives Committee on Appropriations, Subcommittee on Agriculture, Rural Development, and Related Agencies, March 8, 2001.

We urge FDA to properly allocate its limited resources to reduce the overall risk to consumers. FDA could increase the compliance stakes for foreign establishments by more aggressively exercising its prerogative under 21 U.S.C. § 381(a) to refuse entry to products that appear adulterated. Warning Letters and resource consuming formal enforcement efforts are not prerequisites to keeping suspect foreign drug products out of domestic commerce. Exercising this prerogative does not impose a significant burden on the budget and will raise the compliance stakes for foreign manufactures.

Although nearly half of all drugs marketed in the U.S. are produced or manufactured in foreign facilities, and this number is rapidly increasing, the vast majority of FDA inspections occur domestically. Neglecting to adequately inspect foreign drug establishments not only places domestic pharmaceutical manufacturers at an economic disadvantage, it also clearly places U.S. consumers and patients at risk. Contaminated gentamicin from a foreign drug supplier was the apparent cause of seventeen deaths in 1998-1999. Arguably, insufficiently aggressive foreign drug establishment inspections led to the flu vaccine shortage last fall. In order to help protect Americans from facing more crises due to unsafe drugs, the BPTF urges FDA: 1) to utilize its authority to refuse entry under 21 U.S.C. § 381(a) to products that appear adulterated; 2) to rank foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections; 3) to list "foreign facility" as a significant risk factor for purposes of its risk-based approach; and 4) to implement a program of monitoring the impurity profiles of imported over-the-counter (OTC) drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP).

III. ENVIRONMENTAL IMPACT STATEMENT

The action requested does not involve the introduction of any substance into the environment and is subject to categorical exclusion of 21 C.F.R. § 25.30(a) because it involves inspections. To the petitioner's knowledge, no extraordinary circumstances exist.

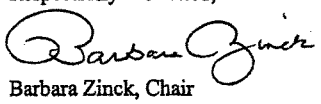
IV. ECONOMIC IMPACT STATEMENT

An economic impact statement is not required at this time.

* * *

The undersigned certify that, to the best of her knowledge and beliefs, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,



Barbara Zinck, Chair
Bulk Pharmaceuticals Task Force

Exhibit 8

Joint Position Paper

"Uneven Enforcement Leads to Sub-par Drugs and National Security Risk"

Submitted by the
European Fine Chemicals Group
and the
Synthetic Organic Chemical Manufacturers Association

The European Union and the United States have rules in place to ensure that Active Pharmaceutical Ingredients (APIs) used to make medicines meet current good manufacturing practices (cGMPs). Compliance with cGMPs is what ensures that each pill and medicated syrup we consume, each injection given to us, and each IV administered to us has the same identity and strength and the same quality and purity characteristics as the product approved by the Health Authorities in EU Member States and in the US.

But not everyone is playing according to the rules, and the American and European public are being put at risk in two critical areas: patient safety and regional/national security.

With regard to patient safety, SOCMA's Bulk Pharmaceutical Task Force (BPTF) submitted formal comments to the U.S. Food and Drug Administration in January 2006 requesting that FDA better manage the public health risk posed by drugs manufactured or processed at foreign facilities.[1] Among the actions requested was to include "foreign facility" as a significant risk factor for purposes of ranking facilities for inspections. As support for its position, the BPTF cite the fact that although more than 80% of APIs used by U.S. manufacturers are imported (about half of the imported volume originates from India and China), FDA inspects foreign suppliers infrequently, if at all.[2] Indeed, FDA's data indicate that in 1999, 242 foreign API manufacturers, in 36 countries, may have exported products to the U.S. without having been inspected by FDA.[3] In 2005 FDA conducted 163 inspections of foreign API manufacturers, of which 14 (9%) of the API inspections were in China, and 23 (14%) were in India, which is not

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[1] Citizen Petition from the Synthetic Organic Chemical Manufacturers Association's Bulk Pharmaceutical Task Force to the U.S. Department of Health and Human Services, Food and Drug Administration, "Petition to Request the Food and Drug Administration to Rank Foreign and Domestic Drug Manufacturing Firms Together for Purposes of the Agency's Risk-Based Approach to Inspections and Take Other Steps to Reduce the Public Health Risks Associated with Imported Drugs" (January 24, 2006) (FDA Docket No. 2006P-0049).

[2] GAO/HEHS-98-21: General Accounting Office, GAO, Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives, Food And Drug Administration, Improvements Needed in the Foreign Drug Inspection Program March 1998; *see also* Prepared Witness Testimony, The House Committee Energy and Commerce, Subcommittee on Oversight and Investigations, June 7, 2001, Prepared Statement of The Honorable Jim Greenwood: http://energycommerce.house.gov/107/hearings/06072001Hearing267/The_Honorable_Jim_Greenwood.htm.

[3] Jane M. Henney, M.D., Testimony to Chairman Fred Upton, Subcommittee on Oversight and Investigations, House of Representatives, October 3, 2000.

proportional to the quantity of API being imported.[4] Former FDA Associate Commissioner William Hubbard is acutely aware of the safety issues presented by this paucity of international inspections. In a May 8, 2006 article in The Washington Post he stated:

> "Most raw materials for our drugs come from foreign producers that are rarely inspected. The rate of quality-control failures found in manufacturing facilities by FDA inspectors has soared. Think your pacemaker, heart valve, microwave oven or morning vitamin was inspected? Dream on."

On the other side of the Atlantic; EU industry groups are equally concerned: Both EFCG and APIC have issued position papers requesting that EU authorities impose greater enforcement of GMPs on API producers[5]. Unlike the USA,[6] the EU is actually unable to say exactly how many factories supply the APIs used to make its medicines. Most of the API inspections performed by EU officials abroad are arranged by the European Directorate for the Quality of Medicines (EDQM).[7] In the 7 years that their inspection scheme has been in operation, 80 API manufacturing sites were inspected with about half in China and India. These inspections yielded 12 suspensions of the Certificates of Suitability (CEP) - from 10 different holders – that had been issued by the EDQM. All 12 suspended CEPs covered API manufacture in China or India. Those CEPs had been relied upon by Medicines Agencies across the EU to approve medicines for sale,[8] but when they were suspended, obviously as a result of serious non-

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[4] Nick Buhay, *Industry/FDA Perspective on Indian and Chinese Quality*, GPhA 2006 API Annual Meeting, New York, New York, March 2006.

[5] See the publications and positions papers at www.efcg.cefic.org (EFCG is a sector group of CEFIC) and www.apic.cefic.org. (APIC is the EU API industry's voice on technical matters.) Both associations operate under CEFIC, the European Chemical Industry Council.

[6] The FDA has a unique numbering system (the NDC number) that makes sure that every label of an API container has a number that describes the "establishment" where the product was made, what product it is and what size packing is labeled. The EU has no such system, thereby making any kind of coordination between EU Medicines Agencies and EU Customs impossible - as a result defending EU borders selectively to keep out non-compliant product is impossible.

[7] The European Directorate for the Quality of Medicines is an institution of the Council of Europe. No other European Institution has done as much as the EDQM to start enforcing GMPs also at Asian producers of APIs.

[8] Presentation by Head of EDQM Certification Unit Corinne Pouget at the EFCG conference, Barcelona 26-27th April 2006, www.efcg.cefic.org EDQM has issued over 2000 Certificates of Suitability, but has inspected no more than 80 producers.

compliance, NO action was taken by the competent authorities - the EU Medicines Agencies have no agreed common procedure on how to act on such notification of suspension.[9] None of the EDQM inspections performed in Europe led to a single CEP suspension.

Today around 80% of the volume of APIs that are used to make the medicines found in EU and US pharmacies come from abroad.[10,11] A large and increasing proportion now comes from countries in Asia, up from close to zero 20 years ago.[12] The vast majority of medicines are no longer produced by the large multinationals; rather, they are products whose patents have expired (generics) and drugs not requiring prescriptions (over the counter drugs or OTCs) that are supplied by a multitude of companies that very often do not make their own APIs but instead buy them from another company.[13] Globalization has caused unprecedented pressure on prices and margins and has driven these generic and OTC companies to buy their APIs at the lowest cost, often from plants that have never been inspected by any health authority from the EU or US. In 2005 alone (Jan to Dec), China -including European owned sites - exported 39,700 metric tonnes of paracetamol; this is a 21% increase over 2004 – enough to produce dozens of billions of tablets.[14] Globalization has resulted in more complex supply chains which increases the

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9 EFCG's "Conclusions" on the Barcelona Conference, 27th – 28th April 2006, http://efcg.cefic.org.

10 Presentation by Jurgen Hoose, Authority for Science and Health, Hamburg, to the 7th APIC/CEFIC European Conference on APIs, Lisbon 20-22 October 2004.

11 EMEA has stated ...approximately 80% of active substances used in the manufacture of medicinal products within the EEA are manufactured outside of the EEA... *in Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials (page 60/101 of Compilation of Community procedures on inspections and exchange of information* http://www.emea.eu.int/Inspections/docs/335103en.doc.

12 See "The world API's market" publication by Dr. Giuseppe Tamburini, Milan, July 2005.

13 Former FDA Commissioner, Dr. Mark McClellan, a strong advocate for generic drugs, in remarks before the First International Colloquium on Generic Medicine on September 25, 2003, said, "Generic drugs now account for the majority of prescriptions in the U.S., and the U.S. has some of the lowest-priced, safe generic drugs available anywhere in the world." He went on to say, "As nations are working hard to find ways to tighten price regulations and shift costs elsewhere, we run a serious risk if product developers don't think they can get a fair payment when they succeed. They will stop trying. They'll turn to products where the prices aren't regulated, like erectile dysfunction drugs and other lifestyle drugs."

14 Reference: "Chinese Paracetamol Export Business Analysis in 2005" by Chinese Medical Export/Import Association, No. 2006-1.

potential for contamination, mislabeling, or substitution of one substance for another all of which increases the risk to patients.[15]

While US-based producers of APIs are inspected by the FDA to assure GMP compliance, APIs made abroad may escape profound inspection and the accompanying scrutiny of their quality control systems. Many EU-based API manufacturers have been inspected by the US/FDA and – in some EU Member States – also by their national authorities. However, in many other parts of the world where API inspection and enforcement has been largely absent, there is no incentive for manufacturers to incur the significant extra costs necessary to meet cGMPs. The problem seems even more serious than "mere" non-compliance with GMP; it appears that even companies in China and India that have been blacklisted by Nigeria's health authorities NAFDAC[16] because of their proven, deep involvement in exporting counterfeit medicines to that country, are still freely exporting APIs to the EU. Thus the health of our citizens is put at risk from sub-standard medicines. FDA has this year issued Warning Letters to some of the leading firms in India.[17] Is this the tip of the iceberg? Are fast growth and compliance difficult to reconcile? Whatever the answer, increased patient risk should never be a consequence of financial success.

The second risk posed by the failure to insist that all companies comply with GMPs relates to regional/national security. By allowing an uneven playing field in which foreign companies benefit while domestic companies suffer, the suffering companies -- if forced to suffer long enough -- go out of business, causing the loss of jobs, tax revenue, and national financial vigor. Even more important: it implies the loss of a secure domestic source of pharmaceuticals in the event of a disruption in one or more of the countries the US and EU are becoming so dependent upon for their pharmaceutical needs – whether caused by terrorism, civil war, pandemic or natural disaster.

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15 DeSorbo, MA. *Balancing Act.* Pharmaceutical Formulation and Quality. 8(2) 2006: 22-24.

16 See http://www.nafdacnigeria.org/blacklisted.html.

17 See warning letters addressed to Wockhardt (February 21) and Ranbaxy (June 15) - CDER's 2006 warning letters under at http://www.accessdata.fda.gov/scripts/wlcfm/indexissuer.cfm.

Applying cGMPs in an industrial setting is complex and expensive. It requires depth and breadth of knowledge and training, plus a great deal of discipline and time. Not meeting cGMPs enables savings that have been estimated at 25% of operating costs (excluding raw materials cost).[18] Compared to domestic facilities, uneven enforcement in foreign facilities means these sites can offer lower cost APIs with only a "voluntary" regard for expensive cGMPs. Paying only cursory attention to cGMPs also allows for greater operational flexibility and faster product development which is a decisive factor in the generics business where the first approval takes all the profits and remains with an enduring market share.[19]

Profit pressures in the generic and OTC drug businesses pit quality assurance departments against the purchasing departments in the same company in an uneven fight. In the absence of a referee, there is a predictable winner every time: the least scrupulous operator. Evidence of the uneven playing field and the resulting financial stress placed on EU and US API suppliers can be seen in the numerous plant closures and staff cut-backs in the last decades.[20,21] If there is a peak in demand triggered by a pandemic or a terrorist event, there will be little domestic production capacity to meet public health needs.

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18 'Managing the Cost of Compliance in Pharmaceutical Operations'; Frances Bruttin & Dr. Doug Dean / IBM Business Consulting Services, April 2004

19 "..in the US Hovione and its customers also lost millions of dollars in sales because Opos-supplied generic firms got their approvals first." January/February 2005 Speciality Chemicals Magazine, page 4, Viewpoint - A Level Playing Field, Guy Villax, CEO of Hovione, calls on the European authorities to inspect API producers abroad.

20 Pharmabiz, an Indian publication, reports that the Environmental Impact Assessment Division (IA) of the Ministry of Environment & Forests has given clearance to about 20 bulk drug projects in the country, since March 2nd 2006, with another 20 projects pending for approval with the IA in "About 40 new bulk drug units coming up in India soon", June 06, 2006, P B Jayakumar, Pharmabiz, Mumbai, India

21 Many of the more traditional APIs such as tetracycline antibiotics and penicillins originally invented and manufactured in the West are today mostly only fermented in China. DSM has now closed down its ex-Gist Brocades penicillin and 6-APA manufacture in Delft. Rhone Poulenc (now Aventis) was once the leading producer of Gentamicin, this product is no longer produced in Europe or the USA, neither is Rifampicin, Lincomycin – and so many others. Today, China makes two thirds of the global production of Penicillin G, the basic intermediate for a large number of essential antibiotics.

The de-localization of API production away from the EU and the US also means our nations are no longer self-sufficient. Neither ciprofloxacin nor doxycycline, which are the front-line treatment for anthrax, are made in the West any more. Every source of every key intermediate is Indian or Chinese.[22] Similar situations exist for the majority of the APIs used to make the drugs that constitute a family physician's basic arsenal to treat the common disorders that afflict our children, grandparents and ourselves.[21]

* * *

In both the EU and the US, government budgets are tight, and inspectors are in short supply. The level of enforcement in many areas is insufficient to ensure a degree of deterrence adequate to maintain quality and standards at a level where risks remain acceptable. SOCMA and EFCG hereby request that the Medicines Agencies / Health Authorities in the US and EU be provided with a mandate and the resources to create a health care environment where all API manufacturers whose product is destined for use by EU or US consumers must comply with cGMPs, regardless of where they are located. When enforcement is adequate, firms are not tempted to use sub-standard APIs and non-compliance ceases to be a competitive advantage. Frequent and random GMP inspections of API producers abroad (or if we need to endure the risks caused by their absence, impurity monitoring as a minimum but inferior surrogate for cGMP inspections) will greatly increase the likelihood that offenders will be caught and public health will be better protected.

Consumers in the EU and the US may benefit from global competition in terms of cost of medicines, but maintaining a minimum level of industrial capacity in key areas is essential to regional/national security. Pharmaceutical production capacity is a key issue from a security standpoint and we urge that steps be taken to stem the loss of domestic API manufacturing

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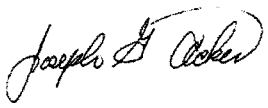
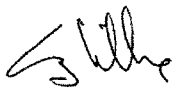
22 « Acetophenone is the key raw material used in the manufacture of ciprofloxacin and DCFB (di chloro fluorobenzene) is the penultimate stage of acetophenone. Out of the six principal manufacturers of DCFB in the world, four are in China and two in India-the Mumbai-based Aarti Industries and Anu's Lab» - Tuesday, August 09, 2005 08:00 IST, Reghu Balakrishnan, Mumbai.

The source for the doxycycline assertion is Hovione, the leading supplier for doxycycline to the West for over 25 years.

facilities. Requiring that foreign facilities meet the same quality standards as EU and US plants, will not, in and of itself, assure that regional/national security is maintained, but rigorous enforcement of the same standards across all pharmaceutical production venues will at least slow the departure to locales where a lack of enforcement results in a lower cost of doing business and a higher risk to the health and safety of EU and US citizens.



Joseph Acker
President
Synthetic Organic Chemical Manufacturers Association



Guy Villax
Chairman, Pharmaceuticals Business Committee
European Fine Chemicals Group, CEFIC, Brussels

Miller, Richard

From: Urwitz, Jay [Jay.Urwitz@wilmerhale.com]
Sent: Tuesday, October 02, 2007 4:36 PM
To: Miller, Richard
Subject: Your Questions

Richard:

(1) The nonprintable AMSCE-000000616 is an attachment to the preceding document (AMSCE-000000615). Document 000615 (from Chris Christopher to Daniel Dayton and others setting up a March 21 teleconference) contains an attachment entitled "meeting.ics," which is an Outlook calendar item. We will include the document in the final production.

(2) The sources for the documents are as follows:

AMSCE 0000001- AMSCE 000000546 (Sept 26, 2007 production): Greg Yurek's hard drive, which included local email and loose files, and a few self-collected items from AMSC.

AMSCE 000000547 - AMSCE 000000823 (October 1, 2007 production): Larry Masur and John Powell email archives; Greg Yurek, John Ulliman, and Larry Masur live email (current email inbox); Marilyn Anderson, Al Baciocco, Blake Bisson, Patricia Carey, Cheri Hart, Nicole Keville, and Charles Stankiewicz documents/files.

Final Production (Forthcoming): Greg Yurek, Larry Masur, and Stuart Karon backup tapes (back to 1/1/06); Jim McGuire and John Ulliman email archives; Linda Taylor, Angelo Santamaria, Nancy Henderson, Joe McNamara documents/files.

(3) I will bring a copy of the calendar with me on Monday for your review. Shall we plan on 11 am or do you want to suggest another time?

Please let me know if you have any further questions.

Best,

Jay

Jay P. Urwitz
WilmerHale
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Washington, DC 20006 USA
+1 202 663 6880 (t)
+1 202 663 6363 (f)
jay.urwitz@wilmerhale.com

Exhibit 10

LEXSTAT 21 USC 360(H)

*** CURRENT THROUGH P.L. 110-80, APPROVED 8/13/2007 ***

TITLE 21. FOOD AND DRUGS
CHAPTER 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT
DRUGS AND DEVICES
DRUGS AND DEVICES

Go to the United States Code Service Archive Directory

21 USCS § 360

§ 360. Registration of producers of drugs and devices

(a) Definitions. As used in this section--
(1) the term "manufacture, preparation, propagation, compounding, or processing" shall include repackaging or otherwise changing the container, wrapper, or labeling of any drug package or package device in furtherance of the distribution of the drug or device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user; and
(2) the term "name" shall include in the case of a partnership the name of each partner and, in the case of a corporation, the name of each corporate officer and director, and the State of incorporation.

(b) Annual registration. On or before December 31 of each year every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices shall register with the Secretary his name, places of business, and all such establishments.

(c) New producers. Every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices in any establishment which he owns or operates in any State shall immediately register with the Secretary his name, place of business, and such establishment.

(d) Additional establishments. Every person duly registered in accordance with the foregoing subsections of this section shall immediately register with the Secretary any additional establishment which he owns or operates in any State and in which he begins the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices.

(e) Registration number; uniform system for identification of devices intended for human use. The Secretary may assign a registration number to any person or any establishment registered in accordance with this section. The Secretary may also assign a listing number to each drug or class of drugs listed under subsection (j). Any number assigned pursuant to the preceding sentence shall be the same as that assigned pursuant to the National Drug Code. The Secretary may by regulation prescribe a uniform system for the identification of devices intended for human use and may require that persons who are required to list such devices pursuant to subsection (j) shall list such devices in accordance with such system.

(f) Availability of registrations for inspection. The Secretary shall make available for inspection, to any person so requesting, any registration filed pursuant to this section; except that any list submitted pursuant to paragraph (3) of subsection (j) and the information accompanying any list or notice filed under paragraph (1) or (2) of that subsection shall

be exempt from such inspection unless the Secretary finds that such an exemption would be inconsistent with protection of the public health.

(g) Exclusions from application of section. The foregoing subsections of this section shall not apply to--

(1) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail;

(2) practitioners licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice;

(3) persons who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in research, teaching, or chemical analysis and not for sale;

(4) any distributor who acts as a wholesale distributor of devices, and who does not manufacture, repackage, process, or relabel a device; or

(5) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that registration by such classes of persons in accordance with this section is not necessary for the protection of the public health.

In this subsection, the term "wholesale distributor" means any person (other than the manufacturer or the initial importer) who distributes a device from the original place of manufacture to the person who makes the final delivery or sale of the device to the ultimate consumer or user.

(h) Inspection of premises. Every establishment in any State registered with the Secretary pursuant to this section shall be subject to inspection pursuant to section 704 [*21 USCS § 374*] and every such establishment engaged in the manufacture, propagation, compounding, or processing of a drug or drugs or a device or devices classified in class II or III shall be so inspected by one or more officers or employees duly designated by the Secretary, or by persons accredited to conduct inspections under section 704(g) [*21 USCS § 374(g)*], at least once in the two-year period beginning with the date of registration of such establishment pursuant to this section and at least once in every successive two-year period thereafter.

(i) Registration of foreign establishments

(1) On or before December 31 of each year, any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States shall, through electronic means in accordance with the criteria of the Secretary, register with the Secretary the name and place of business of the establishment, the name of the United States agent for the establishment, the name of each importer of such drug or device in the United States that is known to the establishment, and the name of each person who imports or offers for import such drug or device to the United States for purposes of importation.

(2) The establishment shall also provide the information required by subsection (j).

(3) The Secretary is authorized to enter into cooperative arrangements with officials of foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether drugs or devices manufactured, prepared, propagated, compounded, or processed by an establishment described in paragraph (1), if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801(a) [*21 USCS § 381(a)*].

(j) Filing of lists of drugs and devices manufactured, prepared, propagated and compounded by registrants; statements; accompanying disclosures.

(1) Every person who registers with the Secretary under subsection (b), (c), (d), or (i) shall, at the time of registration under such subsection, file with the Secretary a list of all drugs and a list of all devices and a brief statement of the basis for believing that each device included in the list is a device rather than a drug (with each drug and device in each list listed by its established name (as defined in section 502(e) [*21 USCS § 352(e)*]) and by any proprietary name) which are being manufactured, prepared, propagated, compounded, or processed by him for commercial distribution and which he has not included in any list of drugs or devices filed by him with the Secretary under this paragraph or paragraph (2) before such time of registration. Such list shall be prepared in such form and manner as the Secretary may prescribe and shall be accompanied by--

(A) in the case of a drug or device contained in the applicable list and subject to section 505 or 512 [*21 USCS § 355* or *360b*] or a device intended for human use contained in the applicable list with respect to which a performance standard has been established under section 514 [*21 USCS § 360d*] or which is subject to section 515 [*21 USCS § 360e*], a reference to the authority for the marketing of such drug or device and a copy of all labeling for such drug or device;

(B) in the case of any other drug or device contained in an applicable list--

(i) which drug is subject to section 503(b)(1) [*21 USCS § 353(b)(1)*], or which device is a restricted device, a copy of all labeling for such drug or device, a representative sampling of advertisements for such drug or device, and, upon request made by the Secretary for good cause, a copy of all advertisements for a particular drug product or device, or

(ii) which drug is not subject to section 503(b)(1) [*21 USCS § 353(b)(1)*] or which device is not a restricted device, the label and package insert for such drug or device and a representative sampling of any other labeling for such drug or device;

(C) in the case of any drug contained in an applicable list which is described in subparagraph (B), a quantitative listing of its active ingredient or ingredients, except that with respect to a particular drug product the Secretary may require the submission of a quantitative listing of all ingredients if he finds that such submission is necessary to carry out the purposes of this Act [*21 USCS §§ 301* et seq.]; and

(D) if the registrant filing a list has determined that a particular drug product or device contained in such list is not subject to section 505 or 512 [*21 USCS § 355* or *360b*], or the particular device contained in such list is not subject to a performance standard established under section 514 [*21 USCS § 360d*] or to section 515 [*21 USCS § 360e*] or is not a restricted device[,] a brief statement of the basis upon which the registrant made such determination if the Secretary requests such a statement with respect to that particular drug product or device.

(2) Each person who registers with the Secretary under this section shall report to the Secretary once during the month of June of each year and once during the month of December of each year the following information:

(A) A list of each drug or device introduced by the registrant for commercial distribution which has not been included in any list previously filed by him with the Secretary under this subparagraph or paragraph (1) of this subsection. A list under this subparagraph shall list a drug or device by its established name (as defined in section 502(e) [*21 USCS § 352(e)*]) and by any proprietary name it may have and shall be accompanied by the other information required by paragraph (1).

(B) If since the date the registrant last made a report under this paragraph (or if he has not made a report under this paragraph, since the effective date of this subsection [effective Feb. 1, 1973]) he has discontinued the manufacture, preparation, propagation, compounding, or processing for commercial distribution of a drug or device included in a list filed by him under subparagraph (A) or paragraph (1); notice of such discontinuance, the date of such discontinuance, and the identity (by established name (as defined in section 502(e) [*21 USCS § 352(e)*]) and by any proprietary name) of such drug or device.

(C) If since the date the registrant reported pursuant to subparagraph (B) a notice of discontinuance he has resumed the manufacture, preparation, propagation, compounding, or processing for commercial distribution of the drug or device with respect to which such notice of discontinuance was reported; notice of such resumption, the date of such resumption, the identity of such drug or device (each by established name (as defined in section 502(e) [*21 USCS § 352(e)*]) and by any proprietary name), and the other information required by paragraph (1), unless the registrant has previously reported such resumption to the Secretary pursuant to this subparagraph.

(D) Any material change in any information previously submitted pursuant to this paragraph or paragraph (1).

(3) The Secretary may also require each registrant under this section to submit a list of each drug product which (A) the registrant is manufacturing, preparing, propagating, compounding, or processing for commercial distribution, and (B) contains a particular ingredient. The Secretary may not require the submission of such a list unless he has made a finding that the submission of such a list is necessary to carry out the purposes of this Act [*21 USCS §§ 301* et seq.].

(k) Report preceding introduction of devices into interstate commerce. Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to the Secretary or person who is accredited under section 523(a) [*21 USCS § 360m(a)*] (in such form and manner as the Secretary shall by regulation prescribe)--

(1) the class in which the device is classified under section 513 [*21 USCS § 360c*] or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified, and

(2) action taken by such person to comply with requirements under section 514 or 515 [*21 USCS §§ 360d, 360e*] which are applicable to the device.

(l) Exemption from reporting requirements. A report under subsection (k) is not required for a device intended for human use that is exempted from the requirements of this subsection under subsection (m) or is within a type that has been classified into class I under section 513 [*21 USCS § 360c*]. The exception established in the preceding sentence does not apply to any class I device that is intended for a use which is of substantial importance in preventing impairment of human health, or to any class I device that presents a potential unreasonable risk of illness or injury.

(m) List of exempt class II devices; determination by Secretary; publication in Federal Register.

(1) Not later than 60 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997 [enacted Nov. 21, 1997], the Secretary shall publish in the Federal Register a list of each type of class II device that does not require a report under subsection (k) to provide reasonable assurance of safety and effectiveness. Each type of class II device identified by the Secretary as not requiring the report shall be exempt from the requirement to provide a report under subsection (k) as of the date of the publication of the list in the Federal Register. The Secretary shall publish such list on the Internet site of the Food and Drug Administration. The list so published shall be updated not later than 30 days after each revision of the list by the Secretary.

(2) Beginning on the date that is 1 day after the date of the publication of a list under this subsection, the Secretary may exempt a class II device from the requirement to submit a report under subsection (k), upon the Secretary's own initiative or a petition of an interested person, if the Secretary determines that such report is not necessary to assure the safety and effectiveness of the device. The Secretary shall publish in the Federal Register notice of the intent of the Secretary to exempt the device, or of the petition, and provide a 30-day period for public comment. Within 120 days after the issuance of the notice in the Federal Register, the Secretary shall publish an order in the Federal Register that sets forth the final determination of the Secretary regarding the exemption of the device that was the subject of the notice. If the Secretary fails to respond to a petition within 180 days of receiving it, the petition shall be deemed to be granted.

(n) Review of report; time for determination by Secretary. The Secretary shall review the report required in subsection (k) and make a determination under section 513(f)(1) [*21 USCS § 360c(f)(1)*] not later than 90 days after receiving the report.

(o) Reprocessed single-use devices.

(1) With respect to reprocessed single-use devices for which reports are required under subsection (k):

(A) The Secretary shall identify such devices or types of devices for which reports under such subsection must, in order to ensure that the device is substantially equivalent to a predicate device, include validation data, the types of which shall be specified by the Secretary, regarding cleaning and sterilization, and functional performance demonstrating that the single-use device will remain substantially equivalent to its predicate device after the maximum number of times the device is reprocessed as intended by the person submitting the premarket notification. Within six months after enactment of this subsection [enacted Oct. 26, 2002], the Secretary shall publish in the Federal Register a list of the types so identified, and shall revise the list as appropriate. Reports under subsection (k) for devices or types of devices within a type included on the list are, upon publication of the list, required to include such validation data.

(B) In the case of each report under subsection (k) that was submitted to the Secretary before the publication of the initial list under subparagraph (A), or any revision thereof, and was for a device or type of device included on such list, the person who submitted the report under subsection (k) shall submit validation data as described in subparagraph (A) to the Secretary not later than nine months after the publication of the list. During such nine-month period, the Secretary may not take any action under this Act [*21 USCS §§ 301* et seq.] against such device solely on the basis that the validation data for the device have not been submitted to the Secretary. After the submission of the validation data to the Secretary, the Secretary may not determine that the device is misbranded under section 502(o) [*21 USCS § 352(o)*] or adulterated under section 501(f)(1)(B) [*21 USCS § 351(f)(1)(B)*], or take action against the device under section 301(p) [*21 USCS § 331(p)*] for failure to provide any information required by subsection (k) until (i) the review is terminated by withdrawal of the submission of the report under subsection (k); (ii) the Secretary finds the data to be acceptable and issues a letter; or (iii) the Secretary determines that the device is not substantially equivalent to a predicate device. Upon a determination that a device is not substantially equivalent to a predicate device, or if such submission is withdrawn, the device can no longer be legally marketed.

(C) In the case of a report under subsection (k) for a device identified under subparagraph (A) that is of a type for which the Secretary has not previously received a report under such subsection, the Secretary may, in advance of revising the list under subparagraph (A) to include such type, require that the report include the validation data specified in subparagraph (A).

(D) Section 502(o) [*21 USCS § 352(o)*] applies with respect to the failure of a report under subsection (k) to include validation data required under subparagraph (A).

(2) With respect to critical or semi-critical reprocessed single-use devices that, under subsection (l) or (m), are exempt from the requirement of submitting reports under subsection (k):

(A) The Secretary shall identify such devices or types of devices for which such exemptions should be terminated in order to provide a reasonable assurance of the safety and effectiveness of the devices. The Secretary shall publish in the Federal Register a list of the devices or types of devices so identified, and shall revise the list as appropriate. The exemption for each device or type included on the list is terminated upon the publication of the list. For each report under subsection (k) submitted pursuant to this subparagraph the Secretary shall require the validation data described in paragraph (1)(A).

(B) For each device or type of device included on the list under subparagraph (A), a report under subsection (k) shall be submitted to the Secretary not later than 15 months after the publication of the initial list, or a revision of the list, whichever terminates the exemption for the device. During such 15-month period, the Secretary may not take any action under this Act [*21 USCS §§ 301* et seq.] against such device solely on the basis that such report has not been submitted to the Secretary. After the submission of the report to the Secretary the Secretary may not determine that the device is misbranded under section 502(o) [*21 USCS § 352(o)*] or adulterated under section 501(f)(1)(B) [*21 USCS § 351(f)(1)(B)*], or take action against the device under section 301(p) [*21 USCS § 331(p)*] for failure to provide any information required by subsection (k) until (i) the review is terminated by withdrawal of the submission; (ii) the Secretary determines by order that the device is substantially equivalent to a predicate device; or (iii) the Secretary determines by order that the device is not substantially equivalent to a predicate device. Upon a determination that a device is not substantially equivalent to a predicate device, the device can no longer be legally marketed.

(C) In the case of semi-critical devices, the initial list under subparagraph (A) shall be published not later than 18 months after the effective date of this subsection. In the case of critical devices, the initial list under such subparagraph shall be published not later than six months after such effective date.

(D) Section 502(o) [*21 USCS § 352(o)*] applies with respect to the failure to submit a report under subsection (k) that is required pursuant to subparagraph (A), including a failure of the report to include validation data required in such subparagraph.

(E) The termination under subparagraph (A) of an exemption under subsection (l) or (m) for a critical or semi-critical reprocessed single-use device does not terminate the exemption under subsection (l) or (m) for the original device.

(p) Electronic registration. Registrations under subsections (b), (c), (d), and (i) (including the submission of updated information) shall be submitted to the Secretary by electronic means, upon a finding by the Secretary that the electronic receipt of such registrations is feasible, unless the Secretary grants a request for waiver of such requirement because use of electronic means is not reasonable for the person requesting such waiver.

HISTORY:

(June 25, 1938, ch 675, Ch. V, Subch A, § 510, as added Oct. 10, 1962, P.L. 87-781, Title III, § 302, 76 Stat. 794; July 15, 1965, P.L. 89-74, § 4, 79 Stat. 231; Oct. 27, 1970, P.L. 91-513, Title II, Part G, § 701(e), 84 Stat. 1282; Aug. 16, 1972, P.L. 92-387, § 3, 86 Stat. 506; May 28, 1976, P.L. 94-295, § 4(a), 90 Stat. 579; Jan. 4, 1983, P.L. 97-414, § 2(b), 96 Stat. 2051; Nov. 21, 1997, P.L. 105-115, Title I, Subtitle B, § 125(a)(2)(C), Title II, §§ 206(a), 209(a), 213(b), Title IV, § 417, 111 Stat. 2325, 2338, 2341, 2347, 2379; June 12, 2002, P.L. 107-188, Title III, Subtitle B, § 321(a), 116 Stat. 675; Oct. 26, 2002, P.L. 107-250, Title II, §§ 201(e), 207, 211, Title III, § 302(b), 116 Stat. 1609, 1613, 1614, 1616; April 1, 2004, P.L. 108-214, § 2(c)(2), 118 Stat. 576.)

HISTORY; ANCILLARY LAWS AND DIRECTIVES

References in text:

The "effective date of this subsection", referred to in subsec. (o)(2)(C), probably means the date of enactment of Act Oct. 26, 2002, P.L. 107-250, which added such subsection.

Explanatory notes:
The bracketed comma has been inserted in subsec. (j)(1)(D) as the punctuation probably intended by Congress.

Amendments:

1965. Act July 15, 1965 (effective 2/1/66 and applicable as provided by § 11 of such Act, which appears as *21 USCS § 321* note), in subsec. (a), redesignated former para. (2) as para. (3), and added para. (2) which read: "The term 'wholesaling, jobbing, or distributing of depressant or stimulant drug to any person who is not the ultimate user or consumer or such drug;"; in subsecs. (b) and (c), inserted "or in the wholesaling, jobbing, or distributing of any depressant or stimulant drug" following "drug or drugs", and added "If any such establishment is engaged in the manufacture, preparation, propagation, compounding, or processing of any such depressant or stimulant drug, such person shall, at the time of such registration, indicate such fact, in such manner as the Secretary may by regulation prescribe." following "establishments." and "establishment.", respectively; and, in subsec. (d), designated the existing provisions as para. (1), and in para. (1) as so designated, deleted the concluding period, inserted "or the wholesaling, jobbing, or distributing of any depressant or stimulant drug. If any depressant or stimulant drug is manufactured, prepared, propagated, compounded, or processed in such additional establishment, such person shall, at the time of such registration, indicate such fact, in such manner as the Secretary may by regulation prescribe." following "devices", and added para. (2), which read: "Every person who is registered with the Secretary pursuant to the first sentence of subsection (b) or (c) or paragraph (1) of this subsection, but to whom the second sentence of subsection (b) or (c) or of paragraph (1) of this subsection did not apply at the time of such registration, shall, if any depressant or stimulant drug is thereafter manufactured, prepared, propagated, compounded, or processed in any establishment with respect to which he is so registered, immediately file a supplement to such registration with the Secretary indicating such fact, in such manner as the Secretary may by regulation prescribe.".

1970. Act Oct. 27, 1970 (effective on the first day of the seventh calendar month beginning after the day immediately preceding enactment on Oct. 27, 1970, as provided by § 704 of such Act, which appears as *21 USCS § 801* note), in subsec. (a), in para. (1), inserted "and" following the concluding semicolon, deleted para. (2) as added by Act July 15, 1965, and redesignated former para. (3), as redesignated by such Act July 15, 1965, as para. (2); and in subsecs. (b), (c), and (d), deleted the matter inserted by Act July 15, 1965; see the 1965 Amendment note.

1972. Act Aug. 16, 1972 (effective on the first day of the sixth month beginning after enactment, as provided by § 5 of such Act, which appears as a note to this section), in subsec. (e), inserted the sentences beginning "The Secretary may also . . ." and "Any number assigned . . ."; in subsec. (f), inserted "; except that any list submitted pursuant to paragraph (3) of subsection (j) and the information accompanying any list or notice filed under paragraph (1) or (2) of that subsection shall be exempt from such inspection unless the Secretary finds that such an exemption would be inconsistent with protection of the public health"; in subsec. (i), inserted "shall require such establishment to provide the information required by subsec. (j) and"; and added subsec. (j).

1976. Act May 28, 1976, in subsec. (a)(1), inserted "or device package", "or device", and "or user" in subsecs. (b), (c), and (d), added "or a device or devices" whenever appearing; in subsec. (e), added the sentence beginning "The Secretary may by regulation . . ."; in subsec. (g), in paras. (1), (2), and (3), inserted "or devices" wherever appearing; in subsec. (h), inserted "every such establishment engaged in the manufacture, propagation, compounding, or processing of a drug or drugs or of a device or devices classified in class II or III"; in subsec. (i), inserted ", or a device or devices" following "drug or drugs", inserted "shall require such establishment to provide the information required by subsection (j) in the case of a device or devices and" and inserted "or devices" following "drugs"; in subsec. (j), in para. (1), in the introductory matter, substituted "a list of all drugs and a list of all devices and a brief statement of the basis for believing that each device included in the list is a device rather than a drug (with each drug and device in each list listed by its established name" for "a list of all drugs (by established name" and substituted "drugs or devices filed" for "drugs filed", in subpara. (A), substituted "the applicable list" for "such list", inserted "or a device intended for human use contained in

the applicable list with respect to which a performance standard has been established under section 514 or which is subject to section 515,", and inserted "or device" following "such drug" wherever appearing, in subpara. (B), in the introductory matter, substituted "drug or device contained in an applicable list" for "drug contained in such list" and substituted cls. (i) and (ii) for ones which read:

"(i) which is subject to section 503(b)(1) a copy of all labeling for such drug, a representative sampling of advertisements for such drug, and, upon request made by the Secretary for good cause, a copy of all advertisements for a particular drug product, or

"(ii) which is not subject to section 503(b)(1), the label and package insert for such drug and a representative sampling of any other labeling for such drug;".

Such Act further, in subsec. (j), in para. (1), in subpara. (C), substituted "an applicable list" for "such list", in subpara. (D), substituted "a list" for "the list", inserted "or the particular device contained in such list is not subject to a performance standard established under section 514 or to section 515 or is not a restricted device", and inserted "or device" following "particular drug product" wherever appearing, in para. (2), in subparas. (A) and (B), inserted "or device" wherever appearing, and in subpara. (C), inserted "or device" wherever appearing and inserted "each" preceding "by established name"; and added subsec. (k).

1997. Act Nov. 21, 1997, in subsec. (j)(1), in subparas. (A) and (D), deleted ", 506, 507," following "505".

Such Act further (effective 90 days after enactment, as provided by § 501 of such Act, which appears as *21 USCS § 321* note), in subsec. (g), redesignated para. (4) as para. (5), added new para. (4), and added the concluding matter; substituted subsec. (i) for one which read: "(i) Foreign establishments. Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices shall be permitted to register under this section pursuant to regulations promulgated by the Secretary. Such regulations shall require such establishment to provide the information required by subsection (j) and shall require such establishment to provide the information required by subsection (j) in the case of a device or devices and shall include provisions for registration of any such establishment upon condition that adequate and effective means are available, by arrangement with the government of such foreign country or otherwise, to enable the Secretary to determine from time to time whether drugs or devices manufactured, prepared, propagated, compounded, or processed in such establishment, if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801(a) of this Act."; in subsec. (k), in the introductory matter, inserted "or person who is accredited under section 523(a)"; and added subsecs. (l)-(n).

2002. Act June 12, 2002 (effective upon the expiration of the 180-day period beginning on enactment, as provided by § 321(c) of such Act, which appears as *21 USCS § 331* note), in subsec. (i)(1), substituted "On or before December 31 of each year, any establishment" for "Any establishment", and substituted "shall, through electronic means in accordance with the criteria of the Secretary, register with the Secretary the name and place of business of the establishment, the name of the United States agent for the establishment, the name of each importer of such drug or device in the United States that is known to the establishment, and the name of each person who imports or offers for import such drug or device to the United States for purposes of importation." for "shall register with the Secretary the name and place of business of the establishment and the name of the United States agent for the establishment."; and, in subsec. (j)(1), in the introductory matter, substituted "(d), or (i)" for "or (d)".

Act Oct. 26, 2002, in subsec. (h), inserted ", or by persons accredited to conduct inspections under section 704(g),"; in subsec. (m)(1), added the sentence beginning "The Secretary shall publish . . ."; and added subsecs. (o) and (p).

2004. Act April 1, 2004, in subsec. (o), in para. (1)(B), substituted "or adulterated" for ", adulterated", and, in para. (2), in subpara. (B), substituted "or adulterated" for ", adulterated", and, in subpara. (E), substituted "semi-critical" for "semicritical".

Redesignation:

This section, enacted as part of Chapter V of Act June 25, 1938, ch 675, became part of Subchapter A of such Chapter as the result of the amendment made by § 2(b) of Act Jan. 4, 1983, P.L. 97-414, which inserted the Subchapter A heading preceding § 501 of Act June 25, 1938, ch 675 (*21 USCS § 351*).

Other provisions:

Congressional declaration of need for registration and inspection of drug establishments. Act Oct. 10, 1962, P.L. 87-781, Title III, § 301, 76 Stat. 793, provided: "The Congress hereby finds and declares that in order to make regulation of interstate commerce in drugs effective, it is necessary to provide for registration and inspection of all establishments in which drugs are manufactured, prepared, propagated, compounded, or processed; that the products of all such establishments are likely to enter the channels of interstate commerce and directly affect such commerce; and that the regulation of interstate commerce in drugs without provision for registration and inspection of establishments that may be engaged only in intrastate commerce in such drugs would discriminate against and depress interstate commerce in such drugs, and adversely burden, obstruct, and affect such interstate commerce.".

Registration of certain persons owning or operating drug establishments prior to Oct. 10, 1962. Act Oct. 10, 1962, P.L. 87-781, Title III, § 303, 76 Stat. 795, provided that any person who, on the day immediately preceding enactment on Oct. 10, 1962, owned or operated an establishment which manufactured or processed drugs, registered before the first day of the seventh month following October, 1962, would be deemed to be registered in accordance with subsec. (b) of this section for the calendar year 1962 and if registered within this period and effected in 1963, be deemed in compliance for that calendar year.

Act Oct. 27, 1970; savings provisions. For a provision that the amendment by Act Oct. 27, 1970 should not affect or abate prosecutions or civil actions commenced prior to the effective date and pending administrative proceedings, see Act Oct. 27, 1970, P.L. 91-513, Title II, Part G, § 702, 84 Stat. 1283, which appears as *21 USCS § 321* note.

Declaration of policy of Drug Listing Act of 1972 [*21 USCS §§ 331, 355, 360*]. Act Aug. 16, 1972, P.L. 92-387, § 2, 86 Stat. 559, provided: "The Federal Government which is responsible for regulating drugs has no ready means of determining what drugs are actually being manufactured or packed by establishments registered under the Federal Food, Drug, and Cosmetic Act [*21 USCS §§ 301* et seq.] except by periodic inspection of such registered establishments. Knowledge of which particular drugs are being manufactured or packed by each registered establishment would substantially assist in the enforcement of Federal laws requiring that such drugs be pure, safe, effective, and properly labeled. Information on the discontinuance of a particular drug could serve to alleviate the burden of reviewing and implementing enforcement actions against drugs which, although commercially discontinued, remain active for regulatory purposes. Information on the type and number of different drugs being manufactured or packed by drug establishments could permit more effective and timely regulation by the agencies of the Federal Government responsible for regulating drugs, including identification of which drugs in interstate commerce are subject to section 505 or 507 [*21 USCS §§ 355, 357*], or to other provisions of the Federal Food, Drug, and Cosmetic Act [*21 USCS §§ 301* et seq.].".

Effective date of Aug. 16, 1972 amendments. Act Aug. 16, 1972, P.L. 92-387, § 5, 86 Stat. 562, provided: "The amendments made by this Act [amending this section and *21 USCS §§ 331* and *335* and adding notes to this section] shall take effect on the first day of the sixth month beginning after the date of enactment of this Act.".

NOTES:

Code of Federal Regulations:

Food and Drug Administration, Department of Health and Human Services--Product jurisdiction, 21 CFR Part 3.

Food and Drug Administration, Department of Health and Human Services--Civil money penalties hearings, 21 CFR Part 17.

Food and Drug Administration, Department of Health and Human Services--Mutual recognition of pharmaceutical good manufacturing practice reports, medical device quality system audit reports, and certain medical device product evaluation reports: United States and the European Community, 21 CFR Part 26.

Food and Drug Administration, Department of Health and Human Services--Protection of human subjects, 21 CFR Part 50.

Food and Drug Administration, Department of Health and Human Services--Financial disclosure by clinical investigators, 21 CFR Part 54.

Food and Drug Administration, Department of Health and Human Services--Institutional review boards, 21 CFR Part 56.

Food and Drug Administration, Department of Health and Human Services--Good laboratory practice for nonclinical laboratory studies, 21 CFR Part 58.

Food and Drug Administration, Department of Health and Human Services--Color additive petitions, 21 CFR Part 71.

Food and Drug Administration, Department of Health and Human Services--Dissemination of information on unapproved/new uses for marketed drugs, biologics, and devices, 21 CFR Part 99.

Food and Drug Administration, Department of Health and Human Services--Food additives permitted in food or in contact with food on an interim basis pending additional study, 21 CFR Part 180.

Food and Drug Administration, Department of Health and Human Services--Labeling, 21 CFR Part 201.

Food and Drug Administration, Department of Health and Human Services--Prescription drug marketing, 21 CFR Part 203.

Food and Drug Administration, Department of Health and Human Services--Registration of producers of drugs and listing of drugs in commercial distribution, 21 CFR Part 207.

Food and Drug Administration, Department of Health and Human Services--Medication guides for prescription products, 21 CFR Part 208.

Food and Drug Administration, Department of Health and Human Services--Current good manufacturing practice for medicated feeds, 21 CFR Part 225.

Food and Drug Administration, Department of Health and Human Services--Over-the-counter (OTC) human drugs which are generally recognized as safe and effective and not misbranded, 21 CFR Part 330.

Food and Drug Administration, Department of Health and Human Services--Antacid products for over-the-counter (OTC) human use, 21 CFR Part 331.

Food and Drug Administration, Department of Health and Human Services--Antiflatulent products for over-the-counter human use, 21 CFR Part 332.

Food and Drug Administration, Department of Health and Human Services--Topical Antimicrobial drug products for over-the-counter human use, 21 CFR Part 333.

Food and Drug Administration, Department of Health and Human Services--Antidiarrheal drug products for over-the-counter human use, 21 CFR Part 335.

Food and Drug Administration, Department of Health and Human Services--Antiemetic drug products for over-the-counter human use, 21 CFR Part 336.

Food and Drug Administration, Department of Health and Human Services--Nighttime sleep-aid drug products for over-the-counter human use, 21 CFR Part 338.

Food and Drug Administration, Department of Health and Human Services--Stimulant drug products for over-the-counter human use, 21 CFR Part 340.

Food and Drug Administration, Department of Health and Human Services--Cold, cough, allergy, bronchodilator. and antiasthmatic drug products for over-the-counter human use, 21 CFR Part 341.

Food and Drug Administration, Department of Health and Human Services--Internal analgesic. antipyretic, and antirheumatic drug products for over-the-counter human use, 21 CFR Part 343.

Food and Drug Administration, Department of Health and Human Services--Topical otic drug products for over-the-counter human use, 21 CFR Part 344.

Food and Drug Administration, Department of Health and Human Services--Anorectal drug products for over-the-counter human use, 21 CFR Part 346.

Food and Drug Administration, Department of Health and Human Services--Skin protectant drug products for over-the-counter human use, 21 CFR Part 347.

Food and Drug Administration, Department of Health and Human Services--External analgesic drug products for over-the-counter human use, 21 CFR Part 348.

Food and Drug Administration, Department of Health and Human Services--Ophthalmic drug products for over-the-counter human use, 21 CFR Part 349.

Food and Drug Administration, Department of Health and Human Services--Antiperspirant drug products for over-the-counter human use, 21 CFR Part 350.

Food and Drug Administration, Department of Health and Human Services--Sunscreen drug products for over-the-counter human use, 21 CFR Part 352.

Food and Drug Administration, Department of Health and Human Services--Anticaries drug products for over-the-counter human use, 21 CFR Part 355.

Food and Drug Administration, Department of Health and Human Services--Miscellaneous internal drug products for over-the-counter human use, 21 CFR Part 357.

Food and Drug Administration, Department of Health and Human Services--Miscellaneous external drug products for over-the-counter human use, 21 CFR Part 358.

Food and Drug Administration, Department of Health and Human Services--Prescription drugs for human use generally recognized as safe and effective and not misbranded: drugs used in research, 21 CFR Part 361.

Food and Drug Administration, Department of Health and Human Services--New animal drugs, 21 CFR Part 510.

Food and Drug Administration, Department of Health and Human Services--New animal drugs for investigational use, 21 CFR Part 511.

Food and Drug Administration, Department of Health and Human Services--Oral dosage form new animal drugs, 21 CFR Part 520.

Food and Drug Administration, Department of Health and Human Services--Food additive petitions, 21 CFR Part 571.

Food and Drug Administration, Department of Health and Human Services--Biological products; general, 21 CFR Part 600.

Food and Drug Administration, Department of Health and Human Services--Licensing, 21 CFR Part 601.

Food and Drug Administration, Department of Health and Human Services--Current good manufacturing practice for blood and blood components, 21 CFR Part 606.

Food and Drug Administration, Department of Health and Human Services--Establishment registration and product listing for manufacturers of human blood and blood products, 21 CFR Part 607.

Food and Drug Administration, Department of Health and Human Services--General biological products standards, 21 CFR Part 610.

Food and Drug Administration, Department of Health and Human Services--General requirements for blood, blood components, and blood derivatives, 21 CFR Part 630.

Food and Drug Administration, Department of Health and Human Services--Additional standards for human blood and blood products, 21 CFR Part 640.

Food and Drug Administration, Department of Health and Human Services--Additional standards for diagnostic substances for laboratory tests, 21 CFR Part 660.

Food and Drug Administration, Department of Health and Human Services--Additional standards for miscellaneous products, 21 CFR Part 680.

Food and Drug Administration, Department of Health and Human Services--Medical device reporting, 21 CFR Part 803.

Food and Drug Administration, Department of Health and Human Services--Medical devices; reports of corrections and removals, 21 CFR Part 806.

Food and Drug Administration, Department of Health and Human Services--Establishment registration and device listing for manufacturers and initial importers of devices, 21 CFR Part 807.

Food and Drug Administration, Department of Health and Human Services--In vitro diagnostic products for human use, 21 CFR Part 809.

Food and Drug Administration, Department of Health and Human Services--Investigational device exemptions, 21 CFR Part 812.

Food and Drug Administration, Department of Health and Human Services--Premarket approval of medical devices, 21 CFR Part 814.

Food and Drug Administration, Department of Health and Human Services--Quality system regulation, 21 CFR Part 820.

Food and Drug Administration, Department of Health and Human Services--Medical device tracking requirements, 21 CFR Part 821.

Food and Drug Administration, Department of Health and Human Services--Clinical chemistry and clinical toxicology devices, 21 CFR Part 862.

Food and Drug Administration, Department of Health and Human Services--Hematology and pathology devices, 21 CFR Part 864.

Food and Drug Administration, Department of Health and Human Services--Immunology and microbiology devices, 21 CFR Part 866.

Food and Drug Administration, Department of Health and Human Services--Anesthesiology devices, 21 CFR Part 868.

Food and Drug Administration, Department of Health and Human Services--Cardiovascular devices, 21 CFR Part 870.

Food and Drug Administration, Department of Health and Human Services--Dental devices, 21 CFR Part 872.

Food and Drug Administration, Department of Health and Human Services--Ear, nose, and throat devices, 21 CFR Part 874.

Food and Drug Administration, Department of Health and Human Services--Gastroenterology-urology devices, 21 CFR Part 876.

Food and Drug Administration, Department of Health and Human Services--General and plastic surgery devices, 21 CFR Part 878.

Food and Drug Administration, Department of Health and Human Services--General hospital and personal use devices, 21 CFR Part 880.

Food and Drug Administration, Department of Health and Human Services--Neurological devices, 21 CFR Part 882.

Food and Drug Administration, Department of Health and Human Services--Obstetrical and gynecological devices, 21 CFR Part 884.

Food and Drug Administration, Department of Health and Human Services--Opthalmic devices, 21 CFR Part 886.

Food and Drug Administration, Department of Health and Human Services--Orthopedic devices, 21 CFR Part 888.

Food and Drug Administration, Department of Health and Human Services--Physical medicine devices, 21 CFR Part 890.

Food and Drug Administration, Department of Health and Human Services--Radiology devices, 21 CFR Part 892.

Food and Drug Administration, Department of Health and Human Services--Records and reports, 21 CFR Part 1002.

Food and Drug Administration, Department of Health and Human Services--Performance standards for electronic products: General, 21 CFR Part 1010.

Food and Drug Administration, Department of Health and Human Services--Performance standards for microwave and radio frequency emitting products, 21 CFR Part 1030.

Food and Drug Administration, Department of Health and Human Services--Performance standards for light-emitting products, 21 CFR Part 1040.

Food and Drug Administration, Department of Health and Human Services--Performance standards for sonic, infrasonic, and ultrasonic radiation-emitting products, 21 CFR Part 1050.

Related Statutes & Rules:

This section is referred to in *21 USCS §§ 331, 352, 353a, 355, 360c, 360e, 360i, 360j, 360m, 360bbb-3, 374, 379h, 379i, 379j-11, 379j-12, 381, 384, 1602, 1604, 1605*; *42 USCS § 1395l*.

Research Guide:

Federal Procedure:

7 Fed Proc L Ed, Consumer Product Safety §§ 16:289, 290.

13 Fed Proc L Ed, Food, Drugs, and Cosmetics §§ 35:175-178, 235, 236, 262, 290, 308, 348.

Am Jur:

25 Am Jur 2d, Drugs and Controlled Substances §§ 104, 107, 133, 139.

Forms:

9A Fed Procedural Forms L Ed, Food, Drugs, and Cosmetics (2006) §§ 31:171-176, 178.

Annotations:

Federal prosecutions based on manufacture, importation, transportation, possession, sale, or use of LSD. *22 ALR3d 1325.*

Law Review Articles:

Legal Aspects of Drug Abuse. *19 Clev St L Rev 461, 1970.*

Responsibility of the Food and Drug Administration under Federal Tort Claims Act. *72 Dick L Rev 580, 1967-68.*

Siegner; Davis. The Animal Medicinal Drug Use Clarification Act of 1994: how will it affect FDA's regulation of animal drugs? 12 Food Drug Cosm & Med Device L Dig 65, September 1995.

Prescription or Ethical Drugs: Fallacies as to Warranties, Failure to Warn, and Strict Liability in Tort. *21 Food Drug Cosm LJ 599, 1966.*

Page; Munsing. Occupational Health and the Federal Government: The Wages Are Still Bitter. *38 Law & Contemp Prob 651, 1973-74.*

Interpretive Notes and Decisions:

1. Generally 2. Relationship with other laws 3. Exclusions

1. Generally

Under circumstances of case, any violation by manufacturer of intramedullary supracondylar nail of *21 USCS § 360* by failing to make proper filings with FDA, had nothing to do, in and of itself, with safety and effectiveness of device as such. *Knoth v Smith & Nephew Richards (1999, CA8 Mo) 195 F3d 355,* CCH Prod Liab Rep P 15673.

Defendant's conviction for felony failing to register drug-manufacturing lab with FDA was upheld, where ample evidence supported conclusion that he acted with intent to defraud or mislead FDA beyond reasonable doubt. *United States v Ellis (2003, CA4 Va) 326 F3d 550.*

Requirement that medical devices manufactured for commercial distribution be listed with Secretary of Health and Human Services is applicable to device for which regulations concerning classification name of device have not been finalized. *United States v Article of Device Consisting of 1,217 Cardboard Boxes (1985, WD Mich) 607 F Supp 990.*

2. Relationship with other laws

Provisions of *21 USCS § 360* do not change state-law tort standard that product manufacturer is not guarantor that no one will get hurt in using product. *Knoth v Smith & Nephew Richards (1999, CA8 Mo) 195 F3d 355,* CCH Prod Liab Rep P 15673.

State-law claims of breach of express warranty and fraudulent concealment filed by knee replacement patient against medical device manufacturer were not preempted by *21 USCS § 360k(a),* part of Medical Device Amendments to Food, Drug, and Cosmetic Act, *21 USCS §§ 360* et seq.; however, supplemental premarket approval (PMA) process for device, unlike notification process under § 360(k), imposed specific requirements sufficient to trigger preemption under § 360k(a) as to state law negligence, strict liability, and breach of implied warranty claims which would have imposed safety and effectiveness requirements on device that, if successful, would have differed from or imposed additional requirements to those requirements established by *FDA. Steele v Depuy Orthopaedics, Inc. (2003, DC NJ) 295 F Supp 2d 439, 52 UCCRS2d 107.*

Former nurse's state law products liability claims against manufacturer of latex gloves were not preempted pursuant to *21 USCS § 360k(a);* pre-market notification process for latex gloves under *21 USCS § 360(k)* did not preempt state law tort claims, and Food and Drug Administration manual concerning latex glove regulatory requirements was not binding regulation. *Adesina v Aladan Corp. (2006, SD NY) 438 F Supp 2d 329.*

Since makers of medical device failed to show that complete preemption exception to well-pleaded complaint rule applied to patient's state law tort claims under Medical Device Amendments of 1976, *21 USCS §§ 360(c)* et seq., case had to be remanded pursuant to *28 USCS § 1447(c);* court was unable to rule on doctor's motion to dismiss on basis that claims examination requirement of *La. Rev. Stat. Ann. § 40:1299.47* had not been met. *Albritton v ABC Corp. (2006, MD La) 451 F Supp 2d 839.*

Unpublished Opinions

Unpublished: Manufacturer's medical device was not entitled to defect-free presumption under *Utah Code Ann. § 78-15-6(3)* because approval manufacturer received pursuant to Medical Device Amendments of 1976 to Federal Food, Drug and Cosmetic Act, codified at *21 USCS § 360(k)*, that of substantial equivalence to pre-1976 device, did not result from its compliance with regulatory standard meeting state's test. *Tingey v Radionics (2006, CA10) 2006 US App LEXIS 20561.*

3. Exclusions

Under *21 USCS § 360(g)(2)* veterinarians may prepare, propagate, compound, or process drugs only from ingredients they lawfully acquire and thus may mix drugs available in 1935 and recognized as safe and effective or drugs that have been approved by FDA where need is great and risk is small, since FDA's reading of its own statute will be accepted to extent there is any doubt and requirement that ingredients be lawfully acquired is implicit in every statute. United States v 9/1 Kg. Containers (1988, CA7 Ill) 854 F2d 173, cert den *(1989) 489 US 1010, 103 L Ed 2d 181, 109 S Ct 1118.*

In in rem seizure action alleging that self-fitting, anti-snoring mouthpiece was adulterated Class III device under *21 USCS § 351(f)(1)(B)*, FDA's decisions were to be reviewed by court under arbitrary and capricious standard, rather than de novo; district court did not err in rejecting manufacturer's counterclaims that FDA acted arbitrarily and capriciously in refusing to exempt mouthpiece from FDA regulation or to clear pre-market notification of mouthpiece under *21 USCS §§ 360(k)* and *360c(f)(1)(A)(ii)*; nor did district court err in refusing to remand case to FDA to consider whether warning label about sleep apnea would be sufficient. *United States v Snoring Relief Labs., Inc. (2000, CA9 Cal) 210 F3d 1081, 2000 CDOS 3412, 2000* Daily Journal DAR 4641.

AIDS patient is denied right to be injected with experimental goat-derived neutralizing antibody drug developed by his doctor, where doctor has not yet acquired FDA approval to use new drug, even though "medical practice exemption" of *21 USCS § 360(g)(2)* does grant limited exception to "registration" requirement for practitioners who prepare drugs solely for use in their own practice, because assertion that this exception provides broad-based exemption to all physicians from requirements of Food, Drug, and Cosmetic Act (*21 USCS §§ 301* et seq.) is incorrect. *Cowan v United States (1998, ND Okla) 5 F Supp 2d 1235.*

Back patient's negligence per se claim based on alleged violation of regulations under *21 USCS §§ 360* et seq. under which Rogozinski Spinal Rod System was marketed must fail, where FDA does not regulate physician's decision to use device for "off-label" use, because patient cannot show that violation of regulations caused her injury since doctor admits he knew Rogozinski device had not been approved for insertion of bone screws in vertebral pedicles, but that he relied on his knowledge of medical standard of care and facts of patient's case in recommending surgery. *Alexander v Smith & Nephew, P.L.C. (2000, ND Okla) 98 F Supp 2d 1287.*

Exhibit 12

FDA Perspective: High Priority Topics & Future Directions

GPhA 2007 Fall Technical Conference
October 10, 2007
Deborah M. Autor, Esq.
Director
CDER Office of Compliance

1

Overview

- CDER OC Mission and Vision
- FDA Modernization: Drug Quality for the 21st Century
- Trends: Recalls, Manufacturing Sites and Inspections
- Foreign Inspections
- Raw Material Control
- FDA's Pharmaceutical Ingredient Safety Task Force
- Bioequivalence Inspections
- Postmarketing Adverse Drug Experience (ADE) Reporting
- Marketed Unapproved Drugs Initiative

2

Mission

Mission (purpose) of the CDER Office of Compliance:

- To promote and protect public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.

3

Vision

Vision (ambition) of the CDER Office of Compliance:

- Through excellence in risk- and science-based policy, surveillance, and enforcement, we prevent consumer exposure to unnecessary risk from drugs throughout their lifecycle.

4

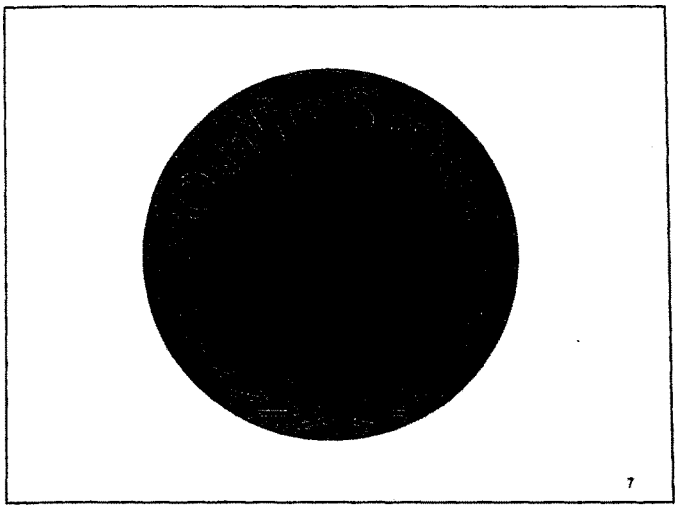
FDA Modernization: Drug Quality for the 21st Century

5

FDA's Quality System Guidance

- Result of the CGMP for the 21st Century Initiative –finalized August 2006
- Encourages the use of modern quality management system for science based manufacturing
- Emphasizes self management of change
- Consistent with overall efforts to reduce manufacturing supplements - 314.70 revisions

6



7

Pharmaceutical Quality Systems ICH Q10

Three new letters to learn as we approach the Desired State for pharmaceutical manufacturing in the 21st Century:

PQS

How did we get here? Are there challenges ahead?

8

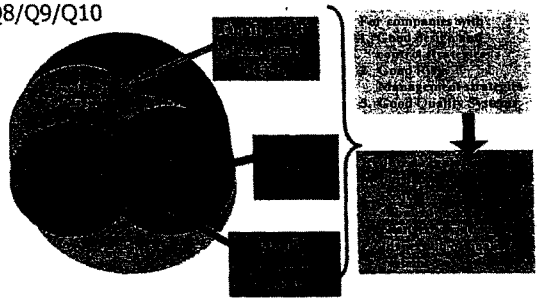
ICH Quality Vision - 2003

- A new vision for ensuring product quality (Brussels, July 2003)
- A harmonized pharmaceutical quality ***system*** applicable across the ***life cycle*** of the product emphasizing an ***integrated*** approach to ***quality risk management and science***
  - New ICH guidelines (high level guidelines, more visionary, less prescriptive, flexible regulatory approaches)
    - Pharmaceutical Development (Q8)
    - Quality Risk Management (Q9)
    - Pharmaceutical Quality Systems (PQS) (Q10)

9

ICH Quality Vision

- Pre-2003: quantitative guidance
- Post-2003: strategic guidance
  - Q8/Q9/Q10



10

ICH Q10 PQS

11

Elements of a Robust Quality System

1. *Science-based* approaches
2. Decisions based on *understanding product's intended use*
3. Proper identification and control of areas of *potential process weakness* (including raw materials)
4. *Responsive deviation and investigation systems* that lead to timely remediation
5. Sound methods for *assessing risk*
6. *Well-defined and designed processes and products,* from development through entire product life cycle.
7. *Systems for careful analyses* of product quality
8. *Supportive management (philosophically and financially)*

12

Integration: CDER and ORA

- How do we more formally transfer our knowledge from Qbd and Qbr from CDER (Review, Compliance) to ORA? Create a "knowledge transfer" from Center to ORA.
  - Similar to technology transfer from R&D to commercial
- Final critical aspect of implementing desired state will be realized by new continuity between CDER and ORA
- Inspectional role:
  - Follow-up on key areas suggested by Center
  - Verify process implementation and state of control
  - Assess lifecycle improvements
  - Ensure adequate change control

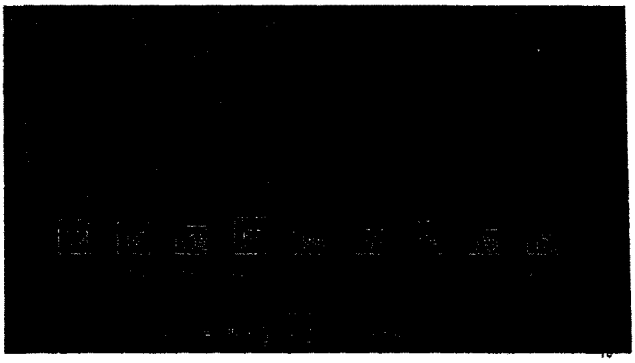
13

Trends

14

Drug Recalls

977 Recalls in FY 2007 (through 9/21)



Drug Recalls

Adjusted to account for multiple-recall incidents

16

Establishment Evaluation Requests (EERs)

- The FD&C Act provides that FDA may not approve an NDA or an ANDA if the facilities and controls used for the manufacture of the drug are inadequate.
- The Office of Compliance serves a role for foreign establishments, similar to a district office
- The site must be evaluated by Office of Compliance with field input prior to approval on a specific PAI or based upon prior CGMP history, unless a product specific PAI is warranted.

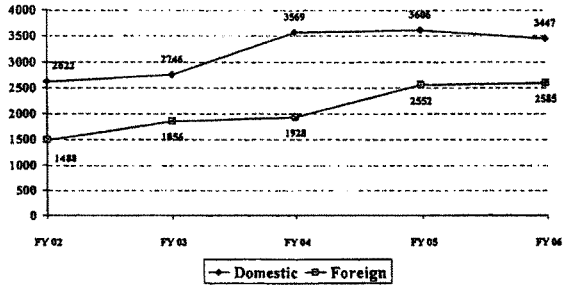
17

Establishment Evaluation Requests (EERs)

- A recent look on a given day this summer in our data base found 231 generic foreign facilities pending an inspection.
- How will this challenge be met? Will the ability to complete timely inspections become a limiting factor in an already challenging generic drug approval queue?
- Up-to-date CGMP surveillance inspection results can help.

18

EERs Submitted for NDAs and ANDAs
(Originals and Supplements)
October 1, 2002 – September 31, 2006

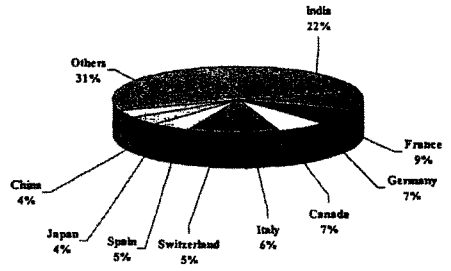


19

Foreign Inspections

20

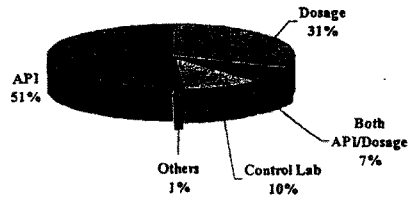
Foreign Inspections by Country in FY 2007*



*FY 2007 data current as of 9/25/07

21

Foreign Inspection in FY 2007* by Firm Type



*FY 2007 data current as of 9/25/07

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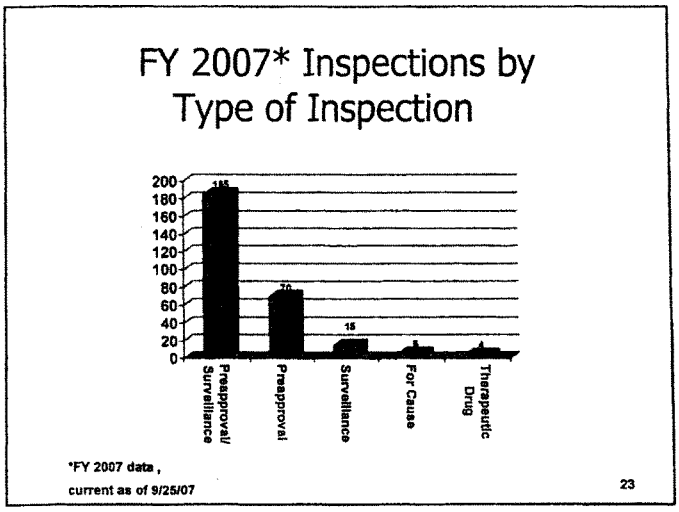
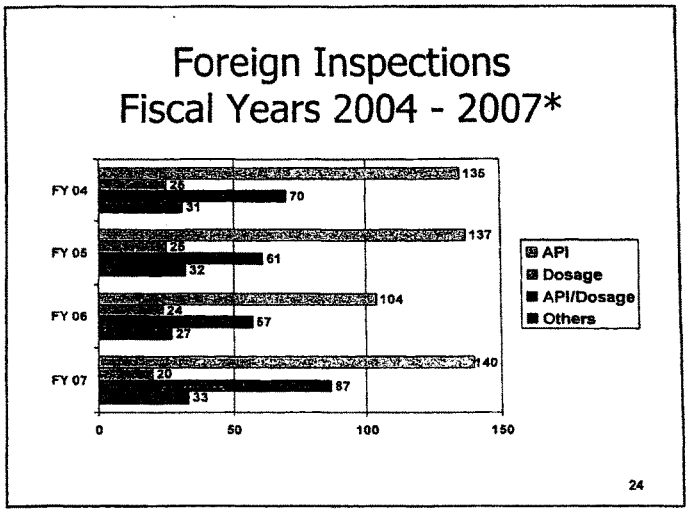
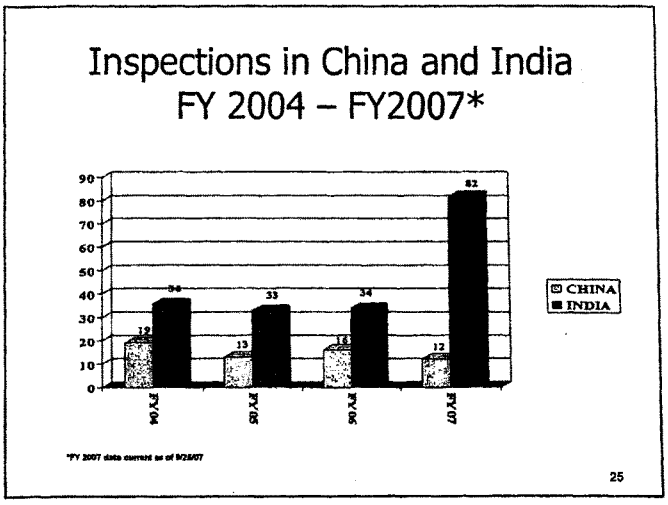
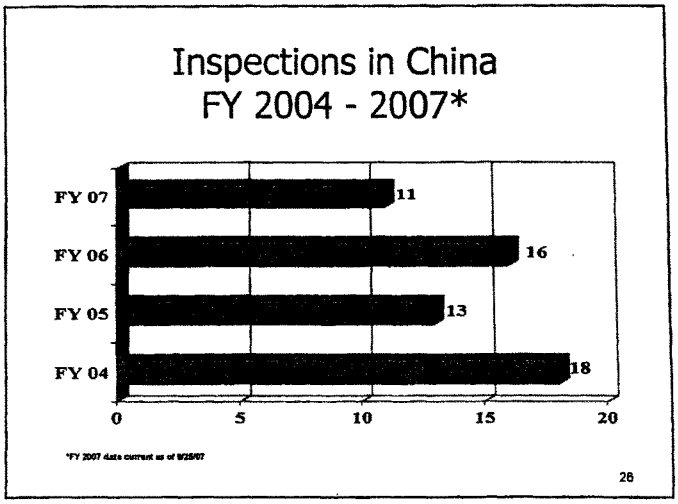

FY 2007* Inspections by Type of Inspection
200
180
160
140
120
100
80
60
40
20
0
185
70
15
Preapproval/ Surveillance
Preapproval
Surveillance
For Cause
Therapeutic Drug
*FY 2007 data , current as of 9/25/07
23


Foreign Inspections Fiscal Years 2004 - 2007*
FY 04
FY 05
FY 06
FY 07
135
26
70
31
137
25
61
32
104
24
57
27
140
20
87
33
0
50
100
150
API
Dosage
API/Dosage
Others
24


Inspections in China and India
FY 2004 – FY2007*
90
80
70
60
50
40
30
20
10
0
12
38
13
33
16
34
12
82
CHINA
INDIA
FY 04
FY 05
FY 06
FY 07
*FY 2007 data current as of 9/25/07
25


Inspections in China
FY 2004 - 2007*
FY 07
FY 06
FY 05
FY 04
11
16
13
18
0
5
10
15
20
*FY 2007 data current as of 9/25/07
26

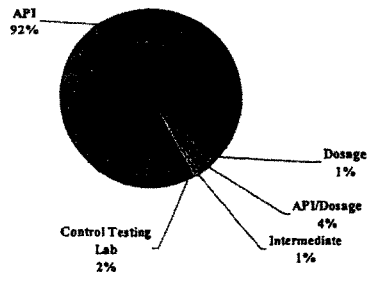
Inspections in China by Firm Type Fiscal Years 2004 – 2007*

FIRM TYPE	FY 04	FY 05	FY 06	FY 07*
API Manufacturer	17	13	15	10
API/Dosage Manufacturer	1	0	0	1
Dosage Manufacturer	0	0	1	0
Total	18	13	16	11

*FY 07 data current as of 9/25/2007

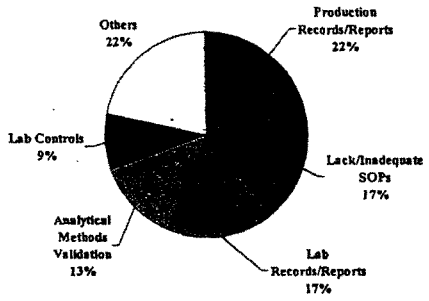
27

Type of Manufacturing Facilities in China



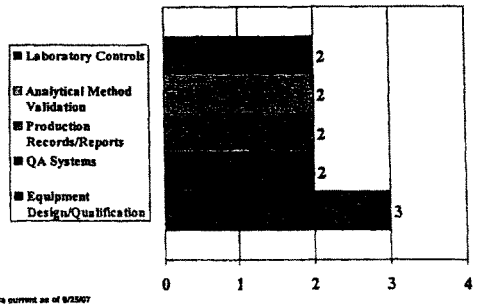
28

Common GMP Deficiencies in China FY 2006



29

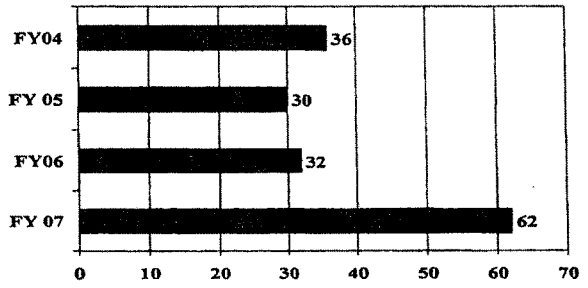
Top Five Deficiencies in China FY 2007*



*FY 2007 data current as of 9/25/07

30

Inspections in India
FY 2004 - 2007*



*FY 2007 data current as of 9/25/07

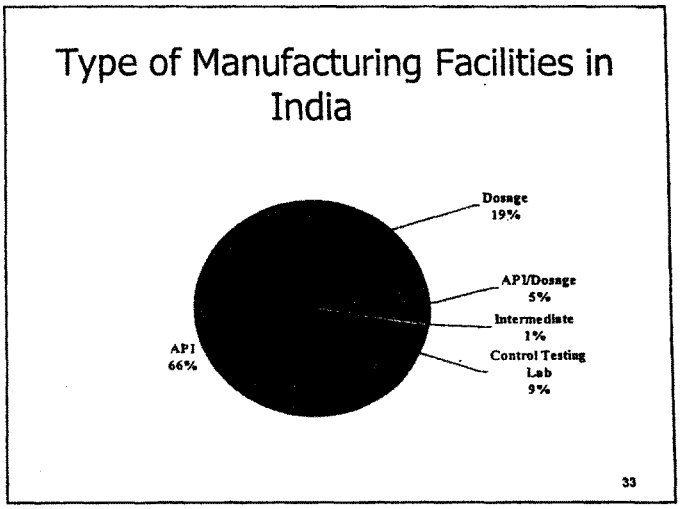
31

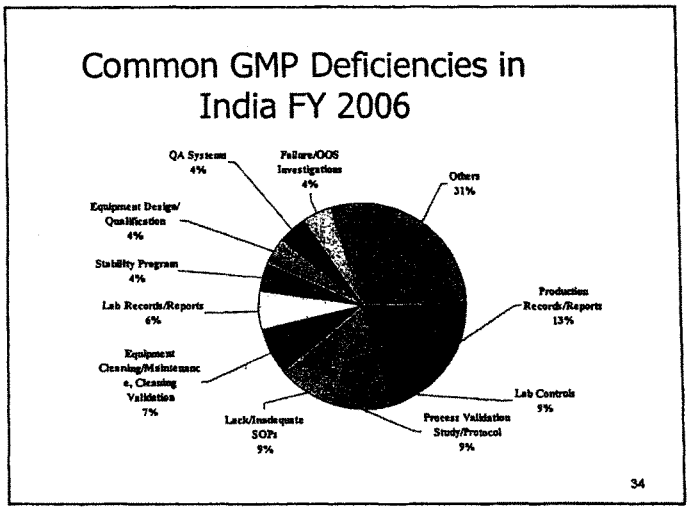
Inspections in India
Fiscal Year 2004 - 2007*

FIRM TYPE	FY 04	FY 05	FY 06	FY 07
API Manufacturer	25	21	16	41
API/Dosage Manufacturer	2	2	6	8
Dosage Manufacturer	6	7	11	14
Contract Lab	3	3	1	6
Totals	36	33	34	62

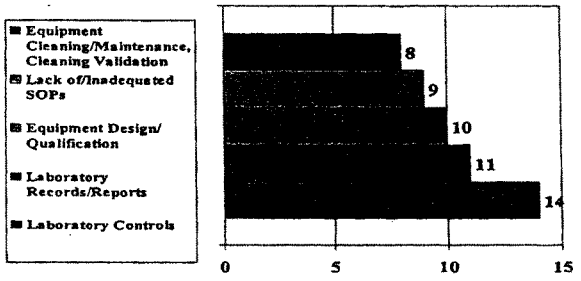
*FY 07 data current as of 9/25/2007

32


Type of Manufacturing Facilities in India
Dosage 19%
API/Dosage 5%
Intermediate 1%
Control Testing Lab 9%
API 66%
33


Common GMP Deficiencies in India FY 2006
QA Systems 4%
Failure/OOS Investigations 4%
Others 31%
Equipment Design/ Qualification 4%
Stability Program 4%
Lab Records/Reports 6%
Production Records/Reports 13%
Equipment Cleaning/Maintenance, Cleaning Validation 7%
Lack/Inadequate SOPs 9%
Process Validation Study/Protocol 9%
Lab Controls 9%
34

Top Five GMP Deficiencies in India FY 2007*



*FY 2007 data current as of 9/25/07

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Raw Material Control

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DEG Contamination

- Scope of the Problem: Recurrent DEG poisoning worldwide (resulting in hundreds of deaths)
  - 2006—Panama
  - 1995-1996—Haiti
  - 1990-1998—Argentina, Bangladesh, India, and Nigeria
  - 1937—United States (Elixir Sulfanilamide)
- **FDA issued guidance in May 2007** to recommend testing and other controls to avoid DEG contamination:
  Guidance for Industry: Testing of Glycerin for Diethylene Glycol

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Guidance on Testing Glycerin for DEG

- Drug product manufacturers should:
  - Perform a specific identity test and a limit of detection test for DEG (the USP limit for DEG is 0.1%)
  - Test all containers of all lots
  - Use the identity tests described in the USP Glycerin Monograph, including the limit test for DEG, or
  - Use an equivalent test, such as the thin-layer chromatography method published in the Journal of AOAC International Vol. 81, No. 1, 1998

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Guidance on Testing Glycerin for DEG

How you can prevent use of DEG-contaminated glycerin:

- Drug product manufacturers should **know the supply chain** for glycerin including the component manufacturer and any distributors. Identify reliable suppliers & know the actual source.
- Manufacturers should **ensure proper testing of glycerin for DEG** and should make personnel aware of the importance of testing and the **potential hazards** if testing is not done.
- Repackers, and others who distribute and prepare glycerin for use in drug products, **should test glycerin used, sold for use, or intended for use in drug products**.
- **Pharmacies** that use glycerin in compounding drug products should either test the glycerin for DEG content or ensure that such testing was properly done by a reliable supplier.

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FDA's Pharmaceutical Ingredient Safety Task Force

40

Pharmaceutical Ingredient Safety Task Force

- DEG/glycerin incidents point out potential risks within global supply chain for ingredients
  - should take measures to anticipate and prevent similar occurrences with other imported ingredients
- FDA formed task force in mid-2007
  - developed recommended action items
  - recommendations seem to be aligned with President's Interagency Task Force initial recommendations regarding import safety publicized this month

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FDA's Pharmaceutical Ingredient Safety Task Force

- Task Force convened by CDER's Office of Compliance in May 2007 to: (cont.)
  - define proactive steps to address risks posed by sourcing poor quality, adulterated and misbranded pharmaceutical raw materials
  - and propose other specific ways to enhance FDA's oversight of pharmaceutical ingredient safety

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What can drug manufacturers do to prevent similar occurrence with any pharmaceutical ingredient?

- Apply quality systems approach to monitor ingredient supply chain integrity
  - Establish a robust supplier qualification program (e.g. audits, quality agreements, appropriate ongoing QC of incoming lots)
  - Only do business with trustworthy sources
  - Verify each ingredient shipment comes from approved suppliers/manufacturers
  - Verify shipments came through expected routes and were not diverted or tampered with
  - Isolate ingredients that are suspected of being non-genuine or mishandled or perhaps adulterated

43

Bioequivalence (BE) Inspections

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Bioequivalence (BE) Inspections

- Verify the quality and integrity of *in vivo* and *in vitro* biopharmaceutics data
  - *in vivo* studies
    - pharmacokinetic BE studies
      - focus on 3 components: clinical, analytical, and statistical
    - clinical endpoint BE studies
      - multi-site studies involving numerous clinical investigators
  - *in vitro* studies
    - e.g., study nasal spray drug products for local action

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BE Program Focus

- Audit studies pivotal to approval decisions
  - generic and innovator drug products
  - PEPFAR applications
    - expedited review process
    - many studies conducted outside U.S.
- Address CDER reviewer concerns about data integrity and study conduct
- Investigate complaints
  - allegations of improper study conduct, fraud

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Inspectional Oversight

- BE program monitors studies from multiple sources
  - contract research organizations (CROs)
  - sponsor facilities
  - clinical investigators
  - academic laboratories
  - sites within and outside the U.S.
  - inspections in India increasing
    - FY02, no BE inspections in India
    - Since FY05, ~50 BE inspections in India

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Problem of Unreliable Data

- Some applications contain unreliable data
  - failure to assure proper dosing
  - study sample contamination not investigated
  - failure to assure data accuracy
  - failure to demonstrate accurate analytical methods
- Consequences
  - FDA rejection of unreliable data
  - unfavorable application outcome
    - can affect multiple applications

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For example – recent action

- Global CRO that conducts pharmacokinetic studies for many pharmaceutical companies
- Studies over a 4-year period from 2 sites were not reliable
- These studies now must be audited or repeated, or specimens must be re-analyzed
- FDA notified affected sponsors
- CDER will monitor follow-up to ensure that approvals and pending applications reflect valid data

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Inspectional Findings

- Examples of deficiencies for generic BE studies include
  - failure to follow protocols and SOPs
  - dosing and reserve sample issues
  - method not adequately validated
  - inappropriate analytical run acceptance
  - inadequate record keeping

50

Goal: Data Quality and Integrity

- Adherence to FDA regulations and guidance is key
- Thoroughly planned and carefully executed studies provide the best chance for success
- Don't ignore problems
  - follow-up investigations are critical to assure suitable study conclusions

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Postmarketing Adverse Drug Experience (ADE) Reporting

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Postmarketing Adverse Drug Experience (ADE) Reporting

- **FDA monitors ADE data reporting by Rx & OTC firms:**
  - NDA/ANDA holders
  - Manufacturers, packers, and distributors whose names appear on drug labels
  - Affiliates, marketing partners, and contractors
- **Compliance assessed through risk-based inspections and surveillance of submissions**

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Postmarketing ADE Reporting (cont.)

- **New FD&C Act requirements for adverse event reporting:**
  - Unapproved OTC and Dietary Supplements
  - Manufacturers, packers, and distributors whose names appear on drug labels
  - Contact information on label
  - All serious events reported within 15 days
  - Guidance soon, effective December 23, 2007
- **Monitoring for compliance begins in FY2008.**

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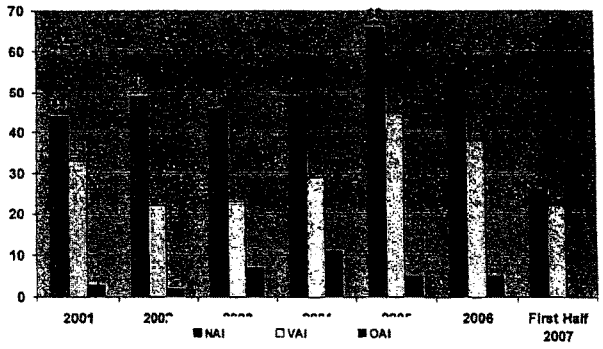
Postmarketing ADE Reporting (cont.)

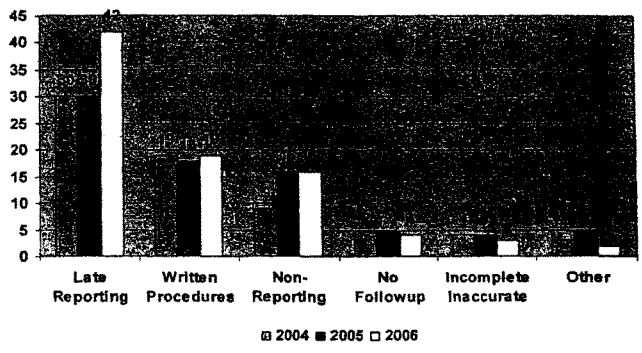
- **FDA reviews:**
  - **Submissions**
    - Complete, Accurate, Timely
    - Postmarketing ADE data
    - Initial and followup individual event reports
    - Periodic summary reports
  - **Pharmacovigilance: Surveillance, Receipt, Evaluation, & Reporting**
    - Written procedures
    - Actual performance
  - **Internal QC/QA and Corrective Actions**

55

Postmarketing ADE Reporting
ADE FY01-FY06 inspectional findings:



Postmarketing ADE Reporting
Cited Deficiencies by Category/Year:



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Postmarketing ADE Reporting (cont.)

- Generic Firms should anticipate receiving increased postmarket ADE data and subsequent FDA monitoring.

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Regulatory Actions vs. Corrective Actions

- Regulatory Action: Legal authority to act to remove the risk by terminating a performance which creates a risk, so that the harmful outcome of the process is not produced. This may stop, but may not correct noncompliance.

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Regulatory Actions vs. Corrective Actions

- Corrective Actions: Identification and reduction of risk by modifying the performance that may create a risk, so that the beneficial outcome of the process can continue to be obtained.
- "Improve the process to improve the product"

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Quality Improvement

- Development and Implementation of Corporate Quality Assurance and Corrective Action can prevent non-compliance.
- Development and Implementation of Quality Assurance and Corrective Actions can avert subsequent regulatory action.

61

Regulatory Meetings

- A meeting requested by FDA management to inform responsible individuals or firms about how products, practices, processes, or other activities violate the law
- A tool to obtain prompt voluntary compliance
  - As a follow-up to a Warning Letter (WL) when firms have not corrected all significant violations
  - To achieve voluntary correction more quickly than through written communication or legal remedies
  - In conjunction with a WL to emphasize the significance of violations

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Marketed Unapproved Drugs Initiative

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Marketed Unapproved Drugs Initiative

- Improve the safety and effectiveness of the nation's drugs
- Encourage companies to comply with the drug approval process, while minimizing disruption to the marketplace
- Provide notice that any product that is being marketed illegally without approval is subject to FDA enforcement at any time

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Marketed Unapproved Drugs Initiative (cont.)

- **June 2006 – Compliance Policy Guide on marketed unapproved drugs explains FDA's risk-based enforcement**
  - Drugs with potential safety risks
  - Drugs that lack evidence of effectiveness
  - Fraudulent drugs
  - Unapproved drugs that directly compete with an approved drug
  - Drugs from firms that otherwise violate the Act (*e.g.*, GMP or ADE reporting violations)
  - Drugs with formulation changes made as a pretext to avoid enforcement

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Marketed Unapproved Drugs Initiative (cont.)

Class-Wide Actions:

- **Hydrocodone** Drug Products (September 2007)
- Timed-Release **Guaifenesin** Drug Products (May 2007)
- Suppository Products Containing **Trimethobenzamide** (April 2007)
- **Ergotamine** Drug Products – Warning Letters (March 2007)
- **Quinine Sulfate** Drug Products **(December 2006)**
- **Carbinoxamine** Drug Products **(June 2006)** 66

Marketed Unapproved Drugs Initiative (cont.)

Enforcement Actions - Specific Firms

- **Syntho/Intermax**
  - GMP violations and unapproved drugs
  - Consent decree
- **Pharmakon Labs**
  - GMP violations and unapproved drugs
  - Court-ordered injunction
- **PharmaFab**
  - GMP violations and unapproved drugs (long history of poor manufacturing practices with repeated failure to institute appropriate corrective action)
  - Consent decree

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Marketed Unapproved Drugs Initiative (cont.)

- **Education**
  - Comprehensive information available on FDA's Unapproved Drugs web site

http://www.fda.gov/cder/drug/unapproved_drugs/default.htm

- **Marketed Unapproved Drugs Workshop (January 2007), Docket # 2003D-0478**
  - Educated firms (especially small firms) on how to obtain approval for their unapproved products
  - Responded to frequently asked questions
  - Participants from more than 150 companies
  - We hope that education and incentives will reduce the need for enforcement

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Summary

- Risk-Based
- Strategic
- Maximizing our impact on the public health

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Exhibit 13

The following information is in response to a request from the House Energy and Commerce Committee regarding Drug Import activities conducted by FDA's Office of Regulatory Affairs (ORA) since Fiscal Year (FY) 2002.

The table below contains excerpts from the FY04-FY08 Congressional Justifications, FDA Field Funding by Functional Activity Table (FAT), Human Drugs Field Activities only. It shows dollars and FTEs for three import categories: Import Laboratory Analyses, Pre- and Post-market Foreign Inspections, and Import Inspections, which include Prior Notice Center security reviews, entry reviews, field exams and other at-the-border activities. Foreign inspections are included because they are considered to be another activity that ORA performs to determine admissibility of products into the United States. Each fiscal year also has a "Total" column for both dollars and FTE for the three categories.

The FAT dollars and FTEs include all the "infrastructure" or support used to conduct the activities described above. This support includes, in addition to import/foreign investigators and laboratory analysts, import entry review functions, the Prior Notice Center, compliance officers, as well as management and IT support for the Field and facility costs.

Note 1: The dollar and FTE for the FY07 and FY08 estimates in the attached table below have been updated from the previous response provided in the July 07 response to reflect the FY07 Revised Continuing Resolution and the related re-basing of the President's FY08 request (Congressional Justification) published in February 2007.

Note 2: ORA does not budget these resources by country.

FDA Field Funding By Functional Activity - Excerpt
DRUGS – FIELD Activities Only

	Premarket Inspections Foreign	Premarket Inspections Foreign	Postmarket Laboratory Analyses Import	Postmarket Laboratory Analyses Import	Postmarket Inspections Foreign	Postmarket Inspections Foreign	Postmarket Inspections Imports	Postmarket Inspections Imports	TOTAL	TOTAL
	$000	FTE	$000	FTE	$000	FTE	$000	FTE	$000	FTE
FY2002 actual	5,732	51	1,106	10	3,349	30	6,527	58	16,714	149
FY2003 actual	5,679	50	1,830	19	3,115	27	6,756	59	17,380	155
FY2004 actual	5,401	48	1,745	18	2,964	26	6,440	55	16,550	147
FY2005 actual	5,385	44	1,740	17	2,955	24	6,421	50	16,501	135
FY2006 actual	4,279	32	2,810	22	3,003	25	6,132	48	16,224	127
FY2007 estimate[1]	4,372	31	3,058	21	3,067	22	4,281	30	14,778	104
FY2008 estimate[2]	5,846	30	2,985	21	2,985	21	4,171	30	15,987	102

[1] FY07 Revised Continuing Resolution

[2] Re-based FY08 Congressional Justification (President's Budget) due to FY07 Revised Continuing Resolution

FDA Funding By Functional Activity - Excerpt DRUGS – Field Activities										
	Premarket Inspections Foreign	Premarket Inspections Foreign	Postmarket Laboratory Analyses Import	Postmarket Laboratory Analyses Import	Postmarket Inspections Foreign	Postmarket Inspections Foreign	Postmarket Inspections Imports	Postmarket Inspections Imports	TOTAL	TOTAL
	$000	FTE	$000	FTE	$000	FTE	$000	FTE	$000	FTE
FY2002 actual	5,732	51	1,106	10	3,349	30	6,527	58	**16,714**	**149**
FY2003 actual	5,679	50	1,830	19	3,115	27	6,756	59	**17,380**	**155**
FY2004 actual	5,401	48	1,745	18	2,964	26	6,440	55	**16,550**	**147**
FY2005 actual	5,385	44	1,740	17	2,955	24	6,421	50	**16,501**	**135**
FY2006 actual	4,279	32	2,810	22	3,003	25	6,132	48	**16,224**	**127**
FY2007 estimate	4,090	31	2,904	22	2,913	22	4,065	31	**13,972**	**106**
FY2008 estimate	5,561	36	2,990	22	2,990	22	4,179	31	**15,720**	**111**

FDA Funding By Functional Activity - Excerpt DRUGS – Field Activities										
	Premarket Inspections Foreign	Premarket Inspections Foreign	Postmarket Laboratory Analyses Import	Postmarket Laboratory Analyses Import	Postmarket Inspections Foreign	Postmarket Inspections Foreign	Postmarket Inspections Imports	Postmarket Inspections Imports	TOTAL	TOTAL
	$000	FTE	$000	FTE	$000	FTE	$000	FTE	$000	FTE
FY2002 actual	5,732	51	1,106	10	3,349	30	6,527	58	**16,714**	**149**
FY2003 actual	5,679	50	1,830	19	3,115	27	6,756	59	**17,380**	**155**
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FY2007 estimate	4,090	31	2,904	22	2,913	22	4,065	31	**13,972**	**106**
FY2008 estimate	5,561	36	2,990	22	2,990	22	4,179	31	**15,720**	**111**

Exhibit 14

RECOMMENDATIONS TO STRENGTHEN SURVEILLANCE AND ENFORCEMENT OPERATIONS ASSOCIATED WITH THE IMPORTATION OF HUMAN DRUGS

INTRODUCTION

The effectiveness of the agency's surveillance and enforcement programs covering imported human drugs is based on two premises. First, FDA conducts inspections of foreign manufacturers or accepts certifications from foreign governments that their plants comply with agency standards and second we examine products offered for entry into the United States. Some ORA manager believe these programs need to be strengthened and this report recommends improvements to achieve this goal.

These recommendations will result in more efficient and effective use of the agency's resources and will establish a more consistant and uniform inspection and enforcement program. Improvements can be made with virtually no additional field resources. All it takes is a more effective utilization of current Field resources in the District offices and greater teamwork between the field, ORO, and CDER. However, we believe that the foreign inspection and import programs need additional resources and that these resources should be funded by proceeds from user's fees.

It is also important that we recognize that several groups inside and outside the agency (GAO, IG, industry associations, and congress) have a keen interest in the level of consistency and uniformity of our surveillance and enforcement programs. Some of these groups are conducting program evaluations to measure the level of consistency and uniformity. We believe that the recommendations contained in this report will strengthen the areas where others might criticize our programs. Likewise, these recommendations to strengthen the foreign inspection and import program will be supported by the domestic pharmaceutical industry, GAO, and members of congress.

THE ISSUES

It is estimated that as high as 70% of the bulk pharmaceutical chemicals (BPC's) used by American plants are imported. Additionally, the number of dosage forms manufactured abroad for the U.S. market is also increasing and there are many factors suggesting that the foreign drug manufacturing industry will continue to grow as many domestic pharmaceutical companies move manufacturing plants off shore. This trend will drive the agency to rely more heavily on its foreign inspection and import surveillance and enforcement programs to assure that American citizens receive human drugs of high quality and purity.

Some field managers believe that ORA has reached a cross-roads in

its quest to manage the increasing number of problems associated with foreigr drug manufacturing plants and imported drugs and with the foreign drug inspection and import programs. We face a number of different opinions and philosophies with members of ORO expecting to create a strong centralized program with most if not all the functions being carried out by an ever increasing headquarters staff. We believe the Center is concerned about it role in MOU's and contacts with foreign government officials. Field managers opt for more decentralization with field and headquarters staff developing partnerships empowering field employees to carry out key functions.

There are powerful incentives to maintain the status quo. There is no question that the issue of "turf" will have to be addressed and overcome if significant changes in our foreign programs are to be implemented. For example, position descriptions might have to be changed. Some people might not have the same ease of access to travel in foreign lands. Some people might loose their ability to deal with foreign government officials. But, none of these issues represent critical issues to the program and they contribute little if anything to efficiency and effectiveness.

There will be arguments that headquarters needs to carry out certain functions to facilitate consistency and uniformity. FDA has used a strong centralized management system for many years as the principle component in its quest to achieve uniformity and consistency; a level playing field for industry. If the complaints we are hearing from industry officials are true, then this strategy has not produced the desired result and some contend that the separation of functions for foreign and domestic surveillance and enforcement programs has led to greater inconsistency.

Having reached this crossroads, it is clear that there is little incentive at lower levels of management to change these very important programs and there is a growing need for top ORA management, and perhaps even the office of the Commissioner, to decide the eventual direction that will be followed in the pursuit of a strengthened foreign inspection and import program. If this is not done, the program will not achieve the level of efficiency and effectiveness that is required and this agency many not be able to assure that American citizens have access to high quality pharmaceuticals.

The Agency has many programs and spends considerable time and money to monitor and assure the quality of drugs manufactured in the United States. Although the foreign supply of all drugs (including BPC's) has increased dramatically, agency programs designed to evaluate the foreign production facilities and foreign product have not grown at the same rate. The increase in the number and amount of drugs imported produces significant pressure on agency programs, but the increases in technology and complexity of some drug manufacturing processes has made an already overburdened system less effective.

History clearly demonstrates that the industry is keenly aware of the regulatory arena in which it operates and for many years the agency's foreign inspection and import programs have offered foreign plants a less rigorous regulatory environment than the domestic enforcement and surveillance programs. This factor may be responsible, in part, for the continued expansion of foreign production of drug products.

Within the past two weeks I have been dealing with one of the worlds largest brand name drug manufacturers. This company is considering the closure of some of its bulk pharmaceutical manufacturing plants in the United States and would then purchase BPC from independent suppliers. This company has sent its quality assurance staff to foreign plants to evaluate the performance of these plants and they have found significant violations of GMP's.

One of the plants that this company visited in China advised them that they had received an inspection in August and that the FDA investigator advised the company that they were "approved" for the drug product under consideration. This statement was not true and a recommendation has been made to withhold approval of this company. This situation caused considerable frustration within the company since the company was operating under the assumption that the agency had approved a facility that it knew was in serious violation of U. S. standards and any good quality control standards. This situation was made more complicated because they were unable to obtain copies of the inspection reports. We were able to clear resolve the issue through good communication.

Perhaps few in the agency have realized the tremendous impact that FD 483's, EIR's, and warning letters have on compliance with GMP's and that this impact extends far beyond the individual plant which is the subject of these documents. This same company mentioned in the foregoing paragraph has advised that the entire industry is using the FD 483, EIR's and warning letters as a means of evaluating foreign plants. A significant complaint we hear from the industry is that foreign reports and FD 483's are not available for several months following an inspection. We have pledged to process these documents in a more timely fashion.

Recently, we have seen too many examples of contaminated and adulterated drugs (even counterfeit drugs) being imported into the United States. As we have learned through FDA history, the lack of agency surveillance and enforcement leads to illegal activities, in addition to adulterated drugs and drugs of low quality. Although the agency has taken steps in early FY'93 to increase the number of foreign inspections and the number of employees assigned to this very important work, more is needed to bring the foreign inspection and import program to the level of regulatory rigor that is given to domestically produced product.

This discussion document addresses some of the issues and concerns about current programs, discusses the current industry, and offers possible solutions to provide better control of the quality of

imported drugs. Additionally, documentation of examples of the problems discussed are submitted to support the statements and conclusions that have been reached. It should be recognized that only some of the examples are presented and that the issues addressed herein represent a general practice rather than isolated cases. For example, we have documented several examples of contaminated drugs made in foreign plants but we have not mentioned all of them in this report.

IMPLEMENTATION OF RECOMMENDATIONS

Some of the recommendations contained in this report will require a significant period of time to achieve. For example, redeployment of resources to different geographical areas will take time, especially when our staff ceiling allow only minimum staffing flexibility. It will take time to develop an OEI and management information reports. Nevertheless, it is recommended that goals and timetables be established to carry out each recommendation that is selected for adoption and that a steering committee be appointed to manage and implement the recommendations.

The steering committee should be chaired by one of more Regional Directors and contain membership from appropriate headquarters and field units. This committee should also include Stephanie Gray. This committee should report directly to Gary Dykstra since the committee will need the authority of the ACRA to carry out its mission.

There may be similar needs for device and food programs. However, there is a need to focus on one product area at a time since is will reduce the number of headquarters units which need to be involved in this project. Once the drug program is implemented, the project can be expanded to other product classes.

It may be important to solicit the support of the Office of the Commissioner since MOU's and other agency wide programs will need to be addressed.

RECOMMENDATION #1--CREATE A FOREIGN DRUG PLANT OEI

We have a statutory obligation to inspect all drug manufacturing plants located in the United States once each two years. We use the agency's OEI of drug plants to manage our inspection obligations. If we are expected to regulate domestic plants in this manner, it seems only reasonable, and fair, that foreign plants shipping product into the United States would be subject to the same conditions and regulatory environment. However, we have no inventory of foreign plants shipping product into the United States and we have no program to evaluate our inspection coverage of these plants. For example, if we need a 25 month alert list for domestic plants, we need one for foreign plants. We don't have one.

ORO has a very limited data base on a P.C. which tracks plants that

have been inspected in the past. This data base could be scanned to locate plants that have been previously inspected and the data used to schedule future inspections. But, there is no means to locate the plants that have never been inspected and this limited data base falls far short of today's needs.

There is some information in the PODS data base, but it appears that we have made little use of it. In order to manage any surveillance program, knowledge of the drugs and manufacturers that are to be controlled is required. It is difficult if not impossible to manage such a diverse and complex foreign drug production industry and the products they produce for the U. S. market without a data base or inventory of active foreign manufacturers, U.S. Agents for these manufacturers, and of bulk drug substances (BPC's) imported. The absence of a data base makes it virtually impossible to manage and coordinate consistent and uniform surveillance and enforcement activities.

There are a number of reasons why an inventory, available to managers throughout the Agency would be of value. Several examples should clarify the need and illustrate the problems:

1) A recent inspection of a public warehouse that stores commercial products, such as televisions, radios, etc. was conducted. One hundred thirty two drums of dipyridamole drug substance (a BPC used to make a coronary vasodilator) were observed labeled that they were made in Shanghi (Shanghi Factory #6). The drums were relocated to this warehouse from another public warehouse approximately one year ago. They were labeled as USP XXI. This was last official in 1990. Additionally, different locks on some of the drums were observed. Other than a copy of the last EIR for Shanghi Factory #6, there is no information available. There is no official file on Shangi Factory # 6 and it would take a significant amount of time to locate the history of Shanghi #6 and to determine if it is an approved supplier of dipyridamole and for which dosage form manufacturers.

2) We recently drafted a Sterile Bulk Inspection Guide. This guide was produced because there have been several recent examples of contaminated sterile bulk drug substances, and there is significant complexity in conducting this type of inspection. While there is a domestic inventory, there is no foreign inventory of these manufacturers that would be applicable to the program. One will find it difficult to identify manufacturers applicable to such a program, what if any recent inspection coverage has been given to the plants, and their regulatory history.

3) We recently inspected a U.S. Agent for a number of foreign manufacturers. In this inspection, we noted that

> the U.S. Agent received seven complaints for contaminated drug substance from three U.S. dosage form manufacturers. The U.S. Agent notified and returned some of the drug substance to the foreign manufacturer. After discussing the complaints and returns with the FDA investigator, who recently conducted a limited foreign inspection of this manufacturer, we concluded that the manufacturer lied to the investigator. The foreign manufacturer did not tell the FDA investigator about the contaminated batches when complaints were discussed. Attempts to identify other substances imported by the manufacturer proved useless. There is no quick way to verify the information provided by the U.S. Agent for drugs imported.

In addition to no active drug plant inventory, the inspection history of foreign plants cannot be readily accessed. For example, in a local follow-up to contaminated sterile antibiotics made in Germany, we found that other foreign sterile antibiotic plants of this company had not been inspected for at least five years. Again, this information was obtained from the U.S. Agent and can only be readily verified using a number of data bases and the personal knowledge of people who have long been associated with the foreign industry. Nevertheless, it is highly unlikely that a sterile antibiotic plant would remain uninspected in the United States for such a long period of time.

FDA has no inventory of U.S. Representatives and responsible personnel for foreign manufacturers and distributors. U. S. Customs law requires a U.S. contact or agent. We view these agents as very important because they conduct business with the agency on behalf of their client. They handle complaints, return product, file official reports such as DMF's and Annual Reports required by FDA regulation, and conduct other basic communications activities.

Action should be initiated to create a foreign official establishment inventory in our PODS data system. This might be somewhat simple in that we can use some of the same data elements that are used for the domestic plants. Once established, we will be able to generate reports, determine the number of inspections per plant, account for the inspection time at given facilities, and we will be able to generate reports for purposes of planning foreign inspection and import coverage and to evaluate the use of our resources.

RECOMMENDATION # 2 ESTABLISH OFFICIAL FILES FOR FOREIGN PLANTS

There are too many different headquarters units handling issues associated with foreign plants without written records being generated and maintained by a single unit. For example, information flows between CDER and foreign health officials regarding the status of foreign plants. This information is obtained for the approval of applications and for other purposes. ORA is rarely aware of these transactions and there is no official file holding the data that pertains to each foreign plant. Indeed

each unit has its own set of files.

The agency has already established the importance of maintaining an official file for each plant in our official establishment inventory. This file is maintained in the field office housing the plant. At the very least we ought to have an official file for each foreign plant shipping product to this country. This file would hold official correspondence such as warning letters, responses to FD 483's, and inspection reports among others. The nature and importance of this file should be recognized by every FDA manager and operating employee.

These files should be maintained in the field district housing the U. S. Representative for the establishment. However, a working file holding important correspondence and other information should be held in ORO. ORO files would facilitate inspection planning and scheduling. This is the same procedure used by the district offices today in that the resident posts maintain a working file in their location.

RECOMMENDATION # 3 INCREASE THE REVIEW OF FOREIGN DMF's

It is recommended that the field investigators conduct a routine review of the DMF's for all foreign inspections to determine if the procedures, formulations, and other critical issues listed in the DMF represent the actual manufacturing processes and controls used to make the product. This review will not duplicate the evaluation of the review of the DMF during the NDA/ANDA evaluation; it will supplement that review in that we will assure that the DMF is current and that the procedures being used to produce the BPC are as listed. It appears from discussions with industry officials and our own investigators that the agency is not making these types of evaluations during current BPC inspections.

The current Drug Master File (DMF) system is cumbersome. From a legal aspect, there are no provisions in the New Drug Regulations for Drug Master Files. The Regulations as written apply to the manufacture and control of both the BPC and dosage form. Thus, a change in the synthesis of the BPC requires that the filing for the dosage form be supplemented, so that the change can be reviewed by the Agency.

We have often found that the DMF file does not reflect the approved process for foreign supplied drug substances. An industry consultant recently commented that they have never seen a DMF actually being followed. (Refer to attachment 6). Some agency reviewers also dislike the current DMF process and there have been suggestions from the industry to improve the system. Gerald Meyer has often stated at meetings with the industry that the agency has no resources to review and approval each DMF submitted to the agency. We must work within the system that we have and we believe this recommendation will strengthen the control of the DMF without a large investment in resources. At the very least we need to assure that the DMF is accurate and authentic and represents

current processes since our review chemists rely on these filings when reviewing and evaluating the BPC listed in an NDA/ANDA.

Although there is considerable dissatisfaction by Agency managers and some in the industry with the current process, foreign suppliers of drug substances seem to be very satisfied with it. We believe this is primarily because there is little, if any, accountability. For example, a manufacturer recently had to return allopurinol drug substance to a plant in Italy (Prosintex) because of foreign metal contamination. This resulted from a complaint by the dosage form manufacturer. The FDA was not notified of the problem and the U.S. Representative who returned the allopurinol to Prosintex, was never notified of the cause or extent of the contamination problem. (Refer to attachment 1 for additional discussions).

The New Drug Regulations require the annual update and reporting of process changes; however, most manufacturers of drug substances do not file annual updates. In a recent inspection of a U.S. Representative for phenytoin, a copy of the current DMF was requested and reviewed. (There are only two approved suppliers of phenytoin). Even though the foreign supplier (Recordati) had a recent inspection, they pointed out that the DMF was being updated to reflect their current process which was not filed.

There was a recent in-depth inspection/evaluation of the DMF filed for the phenytoin made in the U.S. by Warner-Lambert. The foreign manufactured generic substance did not receive the same rigorous evaluation as the brand name product. (Refer to 7/21/93 memo for more detail.)

RECOMMENDATION # 4 PREPARE INSPECTION PROGRAM FOR U.S. REPRESENTATIVES

Our foreign inspection program should be changed to include surveillance and enforcement initiatives at the U. S. Representative level. The filing of an application for a foreign manufacturer requires a domestic agent to communicate with the agency regarding the filing and local issues. In some cases, these agents also act as the broker that processes import (Customs) records. In other situations, these representatives perform other operations, such as repackaging, testing, relabeling, and warehousing the drug. In all cases, a U.S. Representative acts as the focal point for domestic operations and communication.

Our recent inspections of U.S. Representatives has shown that the current foreign inspection program covers only a portion of our potential control of the foreign manufacture of drugs. The agency will need to change its philosophy and include the U. S. Representative as part of its focus on the quality and purity of the foreign product. Thus, the identification of key U. S. Representatives and their responsibilities are an important aspect of the agency's future program to gain much needed information and control of foreign products. For example, the agency recently

issued a Warning Letter to a large multi-national company (Ciba), primarily for GMP deficiencies occurring at their foreign related plants. (Attachment 8 is a copy of the Ciba Warning Letter.) This was achieved without the benefit of a very costly foreign inspection and demonstrates the advantage of working with the U. S. Representative. It also demonstrates the advantage of a domestic evaluation of foreign data.

Regulations provide for control of both the drug substance and the dosage form as it is being manufactured, processed, and controlled. The regulations have always been interpreted to include the manufacturer of the drug substance but, other operations such as shipment, storage, control, and accountability at the U. S. Agent have never been addressed in filings or agency documents. Thus, warehousing of drug substances, processing, labeling, control of damaged bulk containers, reclaim and even salvaging of drug substances, and complaint processing are not covered by any current inspection program. Many of the warehouses used for the storage of drug substances between the filed location for synthesis and alternate dosage form manufacturing location in the U.S. are not inspected.

Many U.S. Representatives maintain a working copy of the filing and they process correspondence between the Agency and the foreign manufacturer. Currently the responsibilities of the U. S. Representative is much better defined in the case of finished dosage forms than for BPC's. For example, it is clear that they are responsible for filing field alerts, processing complaints, reporting adverse reactions, and other key operations for all dosage form drugs. Their responsibilities for the BPC manufacturer have not been well defined at this point. Nevertheless, the agency should expect their responsibilities for both dosage form and BPC products to be the same because the FDC Act applies to both products.

The field has documented counterfeiting of animal drugs and investigations continue with respect to possible counterfeit human BPC's. With greater emphasis being placed on counterfeiting, back-door trading, the agency must hold the U. S. Representative responsible for the importation of product that meets all quality and purity standards established by the ACT. This includes those and those identified in filings as accountable for the movement and storage of drug substances. Additionally, from a GMP aspect, it would seem that the investigation and/or position of reclaims and returns should be documented by the U. S. Representative.

Attachments one through five are summaries of inspections of U.S. Representatives, which depict the many diverse operations and problems that were identified through our domestic local inspections. The foreign inspection program generated little, if any, action regarding domestic operations in these cases. In every inspection of these representatives, we have documented examples of contaminated or defective drugs being imported. This information is valuable for any high quality inspection. The five summaries of inspections attached are representative of the industry.

We have found most representatives to be very cooperative in providing information. However, U. S. Representatives of

independent BPC manufacturers are becoming more guarded in the type of information provided and some have outright refused to provide information. FDA should identify U.S. Representatives, particularly those listed in applications as having filing, communication, and warehousing functions. Files, records, and reports, such as validation reports, compliant files, and many of those records addressed in the Foreign Inspection Guide can therefore, be reviewed before and/or after conducting foreign inspections.

RECOMMENDATION # 5 EVALUATE EIR's IN FIELD RATHER THAN HDQR

Regulatory and other follow up activities covering contaminated product are not the same for foreign and domestic plants and product. Industry officials, members of Congress, and agency managers have all expressed various levels of concern about the issue of uniformity and consistency in the inspection and enforcement programs applied to domestic and foreign drug manufacturing plants. This expression of concern stems from specific instances where there is a demonstrated lack of consistency and uniformity.

These differences involve the rigor of the inspections being conducted in foreign plants and differences in the regulatory follow-up associated with violations of the GMP's and the Act. Many of our largest drug manufacturing companies have plants in the United States and abroad and they have significant experience with the regulatory environment surrounding the operations of their plants in various locations. Perhaps the most significant point to be made in this regard is the one where officials responsible for the domestic plants complain about the "lax" enforcement of GMP's in their foreign plants.

The inconsistent evaluation of the inspection findings and subsequent follow up activity for foreign manufacturing plants is caused by separate units (headquarters and field) reviewing and evaluating the results of inspections and planning follow up strategy to bring violative conditions into compliance. We have noted instances where NDA/ANDA's would be withheld from approval based on significant GMP violations discovered during domestic inspections whereas similar violations found at foreign plants would result in concurrence with approval of applications.

This condition exists for two reasons. First, regulatory follow up and administrative action for foreign plants is being handled by members of the agency with little or no contact and experience with the regulatory follow up assigned to domestic inspection findings. Second, there is a perception that the agency cannot conduct a follow up inspection to assure that corrections have been made because there are insufficient resources to conduct follow up inspections in the future. This leads the agency's headquarters staff to "trust" the foreign firm to correct the violation. In some cases recommendations have been made to CDER to approve applications even though the firm's response stated that corrections would not be made for several months.

The Foreign Inspection Guide, which was implemented on 10-1-92, was discussed at two Commissioner's Exchange Meetings. This guide provides for review of foreign inspections in the field at the

supervisory and management levels. This provision of the guide has not been implemented and was overridden by a headquarters memorandum requiring that these reports be sent to ORO for review.

The headquarters staff believes that they can train their staff in the same manner as the field trains its compliance and supervisory staff. Such goals cannot be achieved since this agency does not often reduce compliance policy to written form. The knowledge and experience of a compliance officer and higher level district management are shaped by the daily contact with headquarters staff where violations of GMP's are being evaluated. At the same time regulatory strategy is constantly changing and field staff plan regulatory strategy and prepare cases for regulatory action. This same level of experience cannot be built into a training program.

The Hoechst Procaine Penicillin case is a good example of differences in compliance activity following the finding of significant violations in foreign and domestic plants. In this case there was essentially no compliance activity nor follow-up to a violative foreign inspection at this foreign plant. However, the investigator who conducted the foreign inspection was from the district housing the domestic U. S. Representative for the foreign company. The investigator continued the inspection of the U. S. Representative on return from the foreign inspection and they (Hoechst-Roussel) recalled marketed batches of foreign product for lack of assurance that the product was sterile.

Another example is the recent Recordati inspection of Dobutamine. The investigator commented on the non-acceptability of the facility but the firm promised to make major facility changes and upgrade the facility and there was a headquarters recommendation to approve the applications even though the promised corrections would not be implemented until several months into the future. If these same violations were discovered in a domestic plant, the field would have recommended withholding approval of the application and we would reinspect before recommending approval of this filing. It is also notable that this firm produced contaminated product which was returned by the U. S. Agent. This contamination was predicted by the conditions documented during the foreign inspection. (Refer to attachment 9.)

The manner in which the field and headquarters handled violative inspections at different Allergan plants for Ofloxacin Ophthalmic Solution, NDA 19-921, is another example of the differences in enforcement strategy. SJN-DO issued a Warning Letter for poor GMP practices. Although similar violations were found in the foreign inspections of two plants, headquarters recommended approval of the pending application because the foreign plants promised to correct the conditions. No further action was taken regarding the foreign plants. (Attached is a summary of the inspections of three Allergan plants.)

District offices are more experienced in processing and continuing investigations activities until all the questions and issues have been addressed. For example, Compliance Branches filter and process a large number of cases on a local level before referring them to CDER Compliance. At the headquarters level, meetings with inspection and compliance personnel, and discussions with foreign

manufacturers rarely occur as a follow-up to foreign inspections. It is far easier to coordinate follow up investigations and activities at the local district level than it is to conduct such activity involving a number of headquarters units and officials. These meetings and follow up activities are common for the domestic industry and are carried out by the local district offices.

In the case of domestic plant inspections evaluations and recommendations are made and reviewed by many different agency managers. Additionally, field compliance branches have more experience in GMP regulatory issues since they process regulatory actions, deal with the Centers, and the General Counsel. Our philosophy is that we should apply the same procedures to foreign inspections as we apply to domestic.

RECOMMENDATION #6 INCREASE DOCUMENTATION IN FOREIGN EIR's

Documentation found in foreign inspection reports is often limited and devoid of basic reporting found in domestic inspection reports. A good example is the coverage of complaints. We are discovering that more documentation is needed in many cases.

For many years our investigators have been taught that they do not have to produce the same level of documentation in foreign inspection reports as for domestic inspections. The rationale for this position is that FDA does not have to take regulatory action against foreign plants the agency has the authority to stop the importation of product from objectionable facilities. This concept may have served us well in previous years, but as stated previously, the industry has changed and it has significantly expanded the amount and the complexity of imported products. We need to obtain enough documentation to facilitate regulatory follow up for product that may already be introduced to the domestic market. This may require seizure if the company (of the U. S. Agent) fails to recall violative product and such action cannot be supported without adequate documentation. For example if Hoechst-Roussel had refused to recall the violative Procaine Penicillin, the agency would have been forced to take regulatory action on a product that had already been entered and released at the port of entry. In this case we would need the same documentation for the foreign product as we would need for the domestic product, if not more.

Another example is the Pierrel EIR which did not cover complaints, nor was there any documentation that complaints were even requested. After a telephone call to the investigator we ascertained that complaints were covered with the firm, and that the firm's managers lied to the investigators and informed them that they received no complaints.

A substantial part of any drug plant inspection is the review of records. Often portions of these reviews are conducted outside the plant. Many GMP problems and potentially objectionable issues are identified during this review process. Obviously, if records are not obtained prior to or during the inspection, then little review can be accomplished. Therefore, we have to increase the amount of documentation of certain violative conditions during our foreign inspections.

Last year, a Foreign Inspection Guide was generated which was intended to provide uniformity between domestic and foreign inspections in the records reviewed and evaluated. The Program or Guide provides for records, such as complaints, validation reports, and many other records to be submitted by the foreign manufacturer prior to our foreign inspection; however, in most cases this has not occurred. Records listed in the Foreign Inspection Guide have in some cases been requested but not received. We believe the requests are too broad and there is a need to focus some of the records requests on certain products and processes. It should be pointed out that the Guide and Agency policy requires that processes for foreign manufacturers be validated prior to the approval of filings.

The request for basic documents, such as validation reports, to be sent to FDA prior to the conduct of a foreign inspection would also reduce the number of foreign inspections. Many foreign manufacturers lack validation reports. For example, Ganes Pharmaceuticals, a large foreign owned plant, has commented that while their domestic operation is in the process of validating their processes, their foreign plant has no purity profiles and has not validated their foreign processes. (Refer to attachment 11 for the Siegfried EIR.)

RECOMMENDATION # 7 INCREASE THE DEPTH AND FREQUENCY OF FOREIGN PLANT INSPECTIONS

The number of inspections planned for each foreign trip should be evaluated. At present these trips begin with too many inspections planned. Planning less inspections per trip will allow the inspection team to increase the depth of the inspection coverage. The inspection trips should be planned with some knowledge of the process and the product which will be inspected. This will require teamwork between the field and ORO personnel and it will require that the field investigators have an opportunity to begin the inspection at the U.S. Representative rather than traveling to the foreign sight with little or no advance preparation.

A well planned inspection trip will require the application of new philosophies and procedures. The current procedure of collecting inspection requests from several sources and then calling the investigator to headquarters for a day or two prior to the trip is insufficient preparation for the inspection and results in inefficient use of agency resources and may reduce overall effectiveness.

The inspection of foreign manufacturers, particularly in the area of bulk drug substance manufacture and particularly sterile bulk manufacturer is significantly different in length, frequency, and depth. For example, inspections over the years of Smith Kline Beecham's sterile bulk facilities have spanned several weeks with significant regulatory action including recalls. An inspection of Wyeth's sterile bulk penicillin facilities required several weeks and resulted in regulatory action including recalls.

As a comparison, we recently inspected Hoechst-Roussel's local facility because of very significant problems identified in their sterile bulk penicillin plant located in Germany. The inspection

was conducted in November 1992. The GMP's at the foreign facility were so bad that only one day was needed at the foreign facility. There was no previous recent inspection of the sterile penicillin manufacturer since 1985. In our review of the DMF, we noted that it has a nine story water for injection system. It is inconceivable how any investigator could conduct such an inspection in less than one week. Fortunately, the facility was so bad that a local follow-up enabled regulatory action (recall) to occur. (Refer to attachment 4 for additional discussion.)

This foreign plant is perhaps the largest sterile drug manufacturing plant in the world and it would take almost a full day just to tour the plant. Typically a domestic plant of this enormous size would receive significant agency attention on a routine basis and it would not be possible for such a facility to remain uninspected for a significant period of time.

Several industry officials and managers who previously worked with FDA and now work in the drug industry point out the gross differences between the depth and length of the domestic and foreign inspections. One only needs to examine the time reported for the domestic and foreign inspections, particularly the bulk drug substance manufacturer. Generally, only 1½ to 2 days are allocated for the foreign inspection of the bulk drug substance manufacturer.

It is often stated that the inspection module for the foreign plant inspections has been significantly increased and that investigators can take additional time if they encounter problems that need additional attention. However, our policy of scheduling an inspection of two days duration with specific schedules to meet in various foreign countries makes it almost impossible for our investigators to deviate from the planned schedule. Most investigators will not request a rescheduling of the inspection trip and will do the best that they can under the circumstances.

An additional concern is that many foreign plant officials have adopted the philosophy that our investigators will only inspect specific products. Our investigators have been faced with resistance when they attempted to expand their scope of coverage beyond the primary product even though other products were being shipped to the United States. Past practice has been a strong teacher.

RECOMMENDATION #8 ASSIGN FOREIGN INSPECTIONS TO DISTRICTS HOUSING THE U. S. AGENT OF THE FOREIGN PLANT

When our resources are sufficiently redeployed, all foreign inspections should begin at the U. S. Representative. There is no question about the large gains in efficiency and effectiveness that can be achieved from this approach.

Approximately one year ago when the Foreign Inspection Guide was generated and discussed, managers of the Foreign Program indicated that they would schedule trips and leave the selection of individuals to district managers. They also said that they would attempt to schedule foreign inspections with the District where the local U.S. Agent resides. This would enable the investigator to

visit and request the records [illegible]
Guide prior to the actual inspection.

In many cases, the investigator has been unaware of the identity of the foreign plants they would be inspecting until several days prior to the inspection when they were "briefed" in Rockville. On two occasions, one of our senior staff was contacted by the U.S. Representative for background on the investigator before the investigator was even made aware of the specific foreign plants they were assigned to inspect. This means the U. S. Representatives are sometimes aware of planned inspections and the investigator who is assigned to the trip before our own staff is aware of the assignment.

This recommendation will discourage operations such as back-door trading and certain illegal activities. It will provide for the collection of meaningful samples of imported substances that will also discourage counterfeiting. This also allows the district with the most knowledge about the company to conduct the inspection.

We should allow the Districts to coordinate and identify the inspection team and shift compliance responsibility to the Districts. This will better utilization agency resources and since these people will handle both domestic and foreign inspections and compliance follow up, more uniformity will be achieved. This will also assure that uniform regulatory follow up will be implemented and managed with the least number of people and units of the agency involved.

RECOMMENDATION #9 INCREASE FIELD ROLE IN MANAGEMENT OF MOU'S

Another major concern with the Foreign Inspection Program is the MOU which prohibits FDA inspection of foreign facilities. In our visits and discussions with many senior managers of large multinational companies, we are advised of major differences in the level of quality between domestic and foreign manufacturing plants. Canada and Switzerland are most often mentioned.

Recently, we conducted an inspection of Ciba (Swiss owned). This was a follow-up to a foreign inspection of one of their contract manufacturing facilities located in Germany. Our inspection of the New Jersey location revealed many significant and objectionable conditions that existed in their manufacturing facilities located in Switzerland. Of greater significance, was the identification of major management problems in Switzerland which had a major impact on the quality of drugs shipped to the U.S. Ciba officials have assured us that Corporate headquarters has agreed to comply with the GMP's. This is the first time that such a statement has been made to us and there is every indication that they will do so.

There is some documentation suggesting that the Swiss government wishes to protect its industry from FDA inspection and regulation through the MOU process. Their refusal to "invite" the agency to conduct an inspection when the agency has specifically identified an interest in conducting an inspection represents a blatant example of their intent. Additionally, it is alleged that meetings have occurred between Swiss officials and members of their industry regarding the subject of FDA inspections. This does not suggest a

cooperative attitude and some are questioning the agency's rationale for maintaining an agreement under these terms.

Inasmuch as there is no formal MOU with this country, steps should be taken to renegotiate the current program. FDA needs to be very open with the Swiss officials and documentation should be prepared before the negotiations begin. We believe that documentation can be obtained from a number of sources and the agency can develop a significant amount of data.

There has been very little management of MOU's. For example there has been no independent audit of the foreign program even though the MOU provides for such audits. Then there is correspondence and communication between CDER and the foreign health officials without ORA being aware of the communication. MOU's and foreign inspections programs should be managed by ORA since ORA is on the cutting edge of manufacturing and process control technology and inspection techniques. Additionally, it is a widely held opinion within the industry that the chief benefit of the MOU program is to isolate the foreign manufacturer from FDA inspection to the disadvantage of the American plants. We do not disagree with this opinion and there is some evidence to substantiate such claims where foreign governments have refused to cooperate with the agency's request to conduct inspections.

Recently, the Agency has pursued regulatory action against Warner-Lambert at all of their domestic locations. In our inspections, we noted that some of the drug products are made by their plant in Canada. We received several field alerts for defective marketed products made by their Canadian plant even though the Canadian regulatory officials had inspected the plant. In order to determine and evaluate the GMP status of products made at their Canadian plant, an inspection was requested and scheduled. The day before the inspection was scheduled to begin, the Center for Drugs Compliance canceled the inspection based on an alleged complaint from the Canadian officials. As of this date, we have given no GMP coverage to their foreign facility, although we are aware that they have major quality problems (recalls and field alerts) for some of the products made at their plant in Canada and have taken legal action against all of the domestic manufacturing locations. Within the past month additional product recalls have occurred, yet no inspection follow-up has been assigned.

This is a clear case where CDER stepped into a situation and decided to cancel an inspection without contacting the ORA unit that had already discussed the inspection with Canadian officials who seemed to be in agreement with the need to evaluate the plant. Following the cancellation of the inspection CDER issued a memorandum to the very person who requested the inspection be conducted. The tone of the memorandum seemed to be saying that we will schedule an inspection if there is a need to do so. This is clear evidence that roles and responsibilities of agency officials needs to be redefined. There is no reason for the ORA organization to justify the need for a foreign inspection, especially when ORA is recognized as the agency organization responsible for implementation of surveillance and enforcement programs.

We are aware of discussions between CDER and Japan regarding an

MOU. Trips have already been arranged and inspection of [illegible] selected by the Japanese have been conducted to demonstrate that they should be granted an MOU. The inspections that were conducted were less than in-depth, broad based inspections which would normally be conducted in our domestic plants. Additionally, there is some concern about the selection of plants for inspection. It would seem that it would be difficult to assess the capability of Japanese health inspectors to provide equivalent inspection coverage especially when their surveillance and enforcement program is still emerging.

Another important issue is the selection of people to conduct the foreign inspections which are needed to justify the signing of and MOU. For example, a CDER official participated in the evaluation of Meiji Seika Kaisha, Ltd., Ashigara, Japan, on a 12/14-18/92 inspection. (Refer to attachment 12 for a copy of the EIR.) He covered the water purification system, heating, ventilation and air conditioning, container washing and sterilizing. Additionally, the inspection report stated that many other areas were given coverage including warehousing, fermentation, purification, clean area, QC Lab, Micro Lab, animal colony, micro assay, labeling, records review, and cleaning procedures. It is virtually impossible to provide inspection coverage of all these operations in the time reported for this inspection location. In fact this was more a plant and quality control tour and briefing than in-depth inspection. Such an in-depth inspection would have taken many days. It is not surprising that the inspection team found no significant objectionable conditions nor is it surprising that a field investigator conducted a scheduled two day inspection on 5/27-28/93 and found significant objectionable conditions in the limited coverage given. (Refer to attachment 13.)

Similarly, in April 1992, CDER conducted several inspections of Swiss manufacturers as part of the Pre-Approval Training Program. One of the inspections included a two day (4/21-22/92) inspection of Siegfried Chemic conducted by CDER with a one day follow-up by another CDER manager. The inspection disclosed that the firm had no active stability program and no impurity profiles. (It is CDER policy that companies are required to document and classify impurities in new drug filings.) Additionally, the 4/29/92 inspection covered acetylcholine. Although there were complaints and validation deficiencies, no FD-483 was issued for this product. More significantly, the EIR was endorsed by IPTSB on 12/5/92 (8 months after the inspection), with the comment that deficiencies are correctable. (Refer to attachment 11.)

More recently a U. S. Representative for foreign BPC manufacturing plants refused to provide documents to an investigator following up on complaints of lack of purity and quality of foreign produced BPC's. The rationale for the refusal in one case is the existence of the Swill MOU. An attorney for this domestic company stated that the agency should request this material through the MOU process and that the domestic company could be violating Swiss law by releasing documents from the Swiss company to the FDA. This incident demonstrates the resolve of Swiss companies to resist FDA examination of their plants and products and it suggests that these actions are being taken with the support of the Swiss government. Perhaps some ORA managers are overreacting, but the number of

events of this nature are increasing and the possibility cannot be ignored.

What is at stake is this agency's ability to investigate complaints and product failures involving foreign products. We now believe that the U. S. Representative bears more legal responsibility for drug product than we first thought possible. Accordingly, steps have already been taken to obtain feedback from General Counsel on this important issue. Additionally, we need to consider the need to detain any drug product that is the subject of complaints unless and until the U. S. Representative has supplied documentation that the problems have been corrected, and that no other products or batches were affected. We do not believe that the agency should be placed in the position of delaying these important inquires until the various levels of government officials have had the time to ponder the issue. It seems a proper role for the U. S. Representative.

Again these are only some of the issues and problems that have been provided to us. We believe that ORA should be given greater responsibility for training foreign investigators, for conducting foreign inspections to evaluate conditions for new MOU's, and for conducting inspections to audit MOU's. There should be more teamwork on these matters. Given the importance of MOU's and the need for a level playing field, the agency should put its most experience investigators and personnel on these types of assignments. While there may be political considerations in each MOU case, the agency has great leverage since most foreign governments see the agreements being more advantageous to their country than to ours. Therefore, the agency should use this great incentive to assure that MOU's are very effective and represent a true benefit to the agency. For example, there is good reason to conclude that this agency is not in control of the Swiss MOU since the Swiss have taken action to refuse inspection by this agency even though the terms of the agreement state that we have the right to inspect. Such action clearly demonstrates a lack of cooperation. Memorandums(attached) dated 12/28/92, and 3/2/93 contain additional examples of problems and discussions. (Refer to attachments 14, 15, and 16.)

We also contend that the inspection of foreign plants to assess MOU's should meet several predetermined criteria and FDA should select the plants to be audited. FDA should use its most experianced investigators to conduct these inspections. They should not be conducted by members of management or headquarters staff with limited current inspection experience.

RECOMMENDATION #10 DISTRICTS SHOULD REVIEW FOREIGN CMC SECTIONS OF THE APPLICATIONS

The triplicate copy of NDA/ANDA's and supplements for foreign plants will be sent to the District having responsibility for the U. S. Representative who filed the application provided there is a domestic plant listed in the application. The NDA/ANDA program managar should review these applications upon receipt for any information that will be required for a pre-approval inspection. This will facilitate more efficient and effective preparation for foreign inspections. Headquarters has access to the copies located

in CDER should they be needed.

RECOMMENDATION #11 REDEPLOY IMPORT INSPECTION RESOURCES AND INCREASE SAMPLING OF IMPORTED DRUGS

There is little, if any, sampling or surveillance testing programs for imported dosage form products and BPC's. Recently, we sampled six lots of an antibiotic at a large U.S. Representative and were told that this is the first time any of their drugs have been sampled by either Customs or FDA. We have found that these representatives store imported drugs in their warehouses before and after release through Customs.

Some products may be adulterated by exposure to non sterile environments and to environments with high levels of humidity. They cannot be readily opened on the docks or in warehouses without some form of environmental control. These drug products should be examined and sampled at the end point user to prevent contamination of the product from the environment. We found a representative warehousing antibiotics for many different dosage form manufacturers. Again, some inventory of U.S. Representatives and warehouses is needed for any sampling program and we must use experienced investigators to carry out this work because the investigator may contaminate a product during the sampling and examination process.

FDA will need to redeploy its import resources to areas where imported pharmaceutical products will be examined and sampled. For example, Newark District has one of the nation's largest concentrations of pharmaceutical plants and has no resources allocated for the import program. Under a new import program, Newark District would be collecting a significant number of samples.

RECOMMENDATION #12 CERTIFY DRUG INSPECTION PERSONNEL

Consistency and uniformity is based on a number of components. Among them is the requirement that all inspection, supervisory, and compliance personnel be equally trained and that they have a minimum level of experience in drug manufacturing and control technology, inspection techniques, and regulatory actions involving GMP violations.

ORA should develop a certification program.

RECOMMENDATION #13 REQUIRE ALL FOREIGN PLANTS AND THEIR U. S. REPRESENTATIVE TO REGISTER WITH FDA

It is highly unlikely that the agency will be able to gain control of the inventory of plants and companies doing business in the United States without an accurate OEI. It is also unlikely that we will be able to establish an accurate OEI without plant registration.

Additionally the drug listing data is insufficient support for the import surveillance program. Foreign distributors often list many drugs which then appear on the drug listing printouts which are

used by our import staff. The origin of some of the [illegible] passing through the hands of these distributors is unknown to our staff when they are evaluated for importation into the United States.

Henry Avallone 9-7-93
Richard J. Davis 9-20-93,
10-4-93
10-15-93
Joe Phillips 9-30-93
Paul D'Eramo 9-30-93
Jim Simmons 10-4-93

Attachments

1. Plantex summary
2. SST summary
3. Recordati summary
4. Hoechst summary
5. Ciba summary
6. Consultant comment
7. 7/21/93 memo
8. Ciba Warning Letter
9. Recordati endorsement
10. Allergan inspection summaries
11. Siegfried FD-483 and EIR
12. Meiji Seika Kaicha 12/14-15/92 EIR
13. Meiji Seika Kaicha 5/31-6/1/93 EIR
14. 8/20/93 memo
15. 12/28/92 memo
16. 3/2/93 memo

Exhibit 15

FDA Scrutiny Scant In India, China as Drugs Pour Into U.S.

Broad Overseas Checks Called Too Costly

By Marc Kaufman
Washington Post Staff Writer
Sunday, June 17, 2007; A01

India and China, countries where the Food and Drug Administration rarely conducts quality-control inspections, have become major suppliers of low-cost drugs and drug ingredients to American consumers. Analysts say their products are becoming pervasive in the generic and over-the-counter marketplace.

Over the past seven years, amid explosive growth in imports from India and China, the FDA conducted only about 200 inspections of plants in those countries, and a few were the kind that U.S. firms face regularly to ensure that the drugs they make are of high quality.

The agency, which is responsible for ensuring the safety of drugs for Americans wherever they are manufactured, made 1,222 of these quality-assurance inspections in the United States last year. In India, which has more plants making drugs and drug ingredients for American consumers than any other foreign nation, it conducted a handful.

Companies based in India were bit players in the American drug market 10 years ago, selling just eight generic drugs here. Today, almost 350 varieties and strengths of antidepressants, heart medicines, antibiotics and other drugs purchased by American consumers are made by Indian manufacturers.

Five years ago, Chinese drugmakers exported about $300 million worth of products to the United States. Eager to meet Americans' demand for lower-cost medicines, they, too, have expanded rapidly. Last year, they sold more than $675 million in pharmaceutical ingredients and products in the U.S. market.

After the pet food scandal that triggered fears over the safety of human and animal foods imported from China, experts say medicines from that country and from India pose a similar risk of being contaminated, counterfeit or simply understrength and ineffective.

"As the manufacturing goes to China and India, the risk to human health is growing exponentially," said Brant Zell, past chairman of the Bulk Pharmaceuticals Task Force. The group represents American drug-ingredient makers that filed a citizen's petition with the FDA last year asking the agency to oversee foreign firms more aggressively.

"The low level there" of follow-up inspections, "combined with the huge amount of importing, greatly increases the potential that consumers will get products that have impurities or ineffective ingredients," he said.

FDA officials say that they are not aware of any health problems caused by drugs imported from India or China and that the American companies that import them usually do their own quality and safety testing. But the agency acknowledges that it is virtually impossible for it to know whether poor-quality or contaminated drugs from lightly regulated Asian plants have caused patients to get sicker or remain ill, especially because patients and doctors are unlikely to suspect poorly manufactured drugs as a problem.

What is clear is that the odds are growing rapidly that the contents of an American medicine cabinet will hold products from the two countries.

Analysts estimate that as much as 20 percent of finished generic and over-the-counter drugs, and more than 40 percent of the active ingredients for pills made here, come from India and China. Within 15 years, they predict, as much as 80 percent of the key ingredients will come from those countries -- which are quickly becoming attractive to brand-name drugmakers, too.

William Hubbard, a former FDA associate commissioner, called the situation dire and deteriorating.

"You have this confluence of events, with so much more product coming from abroad and fewer and fewer inspections," Hubbard said. "This is very serious stuff, because a contaminated drug hitting the market could cause lots of injuries or worse before it got tracked down."

He also said that the FDA inspection system is so weak that many foreign manufacturers believe they "can play games without consequences."

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents many Indian drugmakers, said he would like to see a more permanent FDA presence in his country because "it would help improve standards" and encourage more companies to seek FDA approval of their products.

He said, however, that when U.S. groups raise questions about the quality of India's products, "one must not forget that they may have some agenda," such as protecting their market share. All drugs imported from India, Shah said, come with "assurance of quality, safety and efficacy" from the FDA.

An executive for Shanghai Pharmaceutical, one of China's largest drugmakers, made a similar argument in a recent interview with the U.S. magazine Chemical & Engineering News. He said that all drug ingredients his company exports to the United States meet stringent FDA standards and that American trade groups sometimes "urge quality controls as a trade barrier to protect the interests of their members."

Hubbard and other experts agree that many Indian and Chinese drugmakers are high-quality firms that provide products at a fraction of the price charged by American and European manufacturers. But, they add, Indian and Chinese companies are not only new

to the FDA standards, but they also are in nations that have recent histories of widespread drug counterfeiting, lax quality control and very limited government regulation.

The former head of the Chinese drug and food safety agency, for instance, was recently sentenced to death for taking bribes from companies he regulated, and two major Indian companies received warning letters from the FDA in the past two years over serious infractions involving drug quality control.

Private inspectors hired by U.S. companies to check out foreign plants report finding very good ones but also some without walls and that are open to dust and pests, chemical equipment crowded in ways that could lead to cross-contamination, and one plant that had a hornet's nest atop a drugmaking vat.

One frequently cited case involves the intravenous antibiotic gentamicin, which was supplied by a company in China and linked to deaths in the United States in the late 1990s. Tests by German researchers found a wide range in quality and effectiveness in what were supposed to be uniform dosages of the drug, leading the scientists to write that "it was assumed" the deaths "were related to faulty manufacture."

FDA officials say they have recently begun a risk-based approach to manufacturing oversight -- one that seeks to ensure that drugmakers have proper quality-control systems and that requires fewer inspections. But they acknowledge that financial constraints keep them from making more of the expensive and often hard-to-organize visits to plants in India and China.

"The FDA does the best as it can to regulate overseas good manufacturing practices and do inspections, given the limited resources we have," said Joseph Famulare, deputy director for international inspections. "If we had more resources, we would get more inspections done."

Despite repeated requests for information about the FDA's budget for overseas drug inspections, the agency did not make it available.

India and China are hardly the only nations manufacturing drugs and active ingredients for the American market: The Commerce Department reported that more than $42 billion in drugs and drug ingredients were imported last year.

Most of the other suppliers are in Europe, Japan and Singapore, however, and many have a long track record of working with U.S. drug companies and regulators. Other than Israel, which has a booming drug export industry, India and China are the fastest-growing suppliers of low-cost drugs and are poised, analysts said, to grow faster.

Their niche is primarily the quickly expanding market for generic drugs, which account for more than 60 percent of prescriptions filled in the United States. Analysts with Newport Strategies, a drug-information-gathering and consulting firm that works extensively in India and China, report that Indian firms won FDA approval to import

more than 100 generic drugs last year. Drug analyst Utkarsh Palnitkar of Ernst & Young in Hyderabad, India, said Indian firms accounted for more than 20 percent of FDA generic drug approvals last year, compared with less than 7 percent five years ago.

A similar dynamic can be seen in the drug "master files" reviewed by the FDA. These documents are submitted when a firm wants to sell "active pharmaceutical ingredients" to American companies.

In 1999, India did not appear on an FDA chart of master files. By 2004, almost half of the reviewed files for drug ingredients destined for U.S. patients came from Indian companies. More recently, Indian companies have moved more aggressively into making finished drugs, and Chinese companies -- which expect as many as 4,000 international buyers at a series of drug ingredient conferences in Shanghai this month -- have expanded their share of the market in active ingredients.

"The last two years were the tipping point when it comes to Indian finished drugs," said Michael Chace-Ortiz, senior director of Newport Strategies. "They still dominate here" with active pharmaceutical ingredients, "but finished generic drugs are their future," he said. "And as they move up the chain, the Indians themselves have begun to buy active ingredients from the Chinese."

China, for instance, specializes in making ingredients for antibiotics, which are often made into capsules in India and exported to the United States and elsewhere.

In addition to the United States' $675 million in pharmaceutical imports from China last year, India sold $800 million worth of finished drugs and ingredients here in 2006, according to Commerce Department records.

Yet on-the-ground inspections of Indian and Chinese plants remain rare and relatively brief and are always scheduled in advance, unlike the surprise visits that FDA inspectors pay to domestic manufacturers. FDA records show that 32 inspections were carried out last year in India, and most were for companies seeking approval to sell a drug or ingredients, not to check on the quality of manufacturing. Fifteen visits were made to Chinese plants.

Even these small numbers overstate the FDA's oversight. Some of the 32 India inspections -- the agency would not say how many -- involved drugs that, by law, cannot be sold to Americans. They were to review companies that wanted to take part in President Bush's program to supply cheap AIDS drugs to Africa.

FDA officials say U.S. drugmakers regularly test the drugs and active ingredients they buy from abroad, and industry officials say such testing -- which includes the all-important determination that the generic drugs are "bioequivalent" to brand-name products -- is essential to protect their reputations and often substantial capital investments.

But the generic-drug business is fiercely competitive, and the key to success often is providing the least expensive product -- a pressure on prices that has allowed Wal-Mart to sell almost 200 generic drugs for a flat $4-per-prescription fee. Some experts worry that, to cut costs, expensive quality-control systems are being shortchanged.

That was the case at Able Laboratories, a once highflying New Jersey maker of generic drugs with close ties to India. It went bankrupt two years ago. FDA inspectors found that some of its quality-control data had been falsified, leading to one of largest drug recalls in FDA history. This year, four Able employees pleaded guilty to criminal charges of fraud.

Last year, two of India's largest and most respected drugmakers, Ranbaxy Laboratories and Wockhardt, received FDA warning letters about quality-control and documentation issues at their Indian plants. Both companies were told that if they did not improve, some of their Indian-made products would be barred from the United States.

In February, the FDA's Office of Criminal Investigations raided the New Jersey offices of Ranbaxy. The FDA would not comment on the raid, and the company has said it is cooperating with the agency. A company spokesman said that the FDA was conducting "a wide dragnet," and a source familiar with the investigation said that it involved an unusually large number of investigators.

Because of U.S. drugmakers' concerns over quality control, U.S. Pharmacopoeia -- a nonprofit organization that works with drugmakers and regulators to set drug-quality standards -- opened an office in Hyderabad, a center of the Indian drug industry. Executive Director Roger Williams said Dr. Reddy's Laboratories recently became the first Indian firm to agree to pay USP to check the quality of its products.

"The question is whether the perishingly low price of generics is making it impossible to get quality," Williams said. "It's the job of the FDA to make sure that doesn't happen, and I'm concerned that they just don't have the resources to get people over to places like India frequently enough."

Staff writer Mary Pat Flaherty and staff researcher Madonna Lebling contributed to this report.

Exhibit 16

Health, Money & Education

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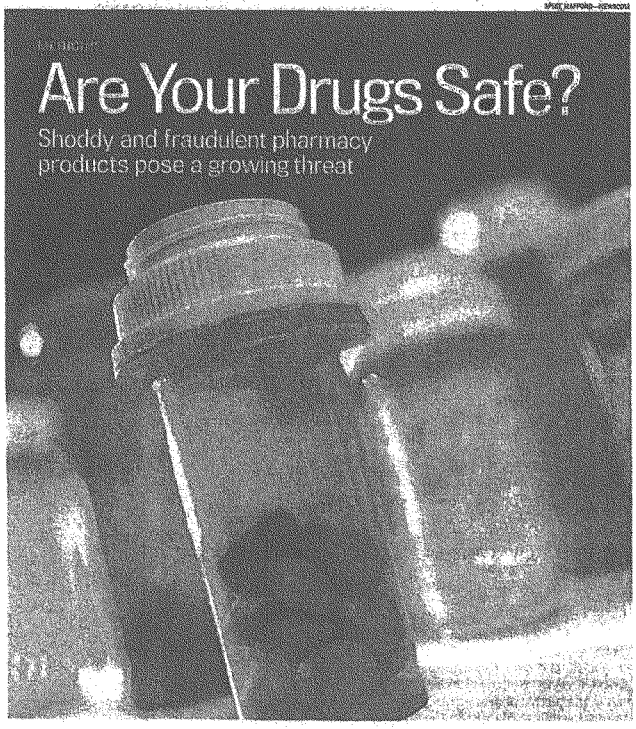


Are Your Drugs Safe?

Shoddy and fraudulent pharmacy products pose a growing threat

By Nancy Shute

Warning: The contents of your medicine cabinet may not be what they seem.

Just 10 of the 21 multivitamins tested met the quality claims on the label, ConsumerLab.com of White Plains, N.Y., reported in January. Several had significantly more or less of the active ingredients than promised; one was contaminated with lead.

Last fall, more than 1 million counterfeit OneTouch diabetes test strips flooded the United States and went on sale in 700 pharmacies in 35 states.

And in December, metal poisoning took the life of a 58-year-old woman who lived on Vancouver Island, Canada. Prescription medications she had purchased from an Internet pharmacy contained toxic amounts of aluminum.

"How is anybody supposed to know the difference?" asks Arthur Soclof, an allergist in Livonia, Mich. He discovered that the Lipitor he'd bought at his local pharmacy was fake only because the pills wouldn't break the way they had in the past. "If I wasn't splitting pills I wouldn't have thought twice about it," says Soclof, 50.

Gone are the days when Americans could unquestioningly trust in the quality and authenticity of their pharmaceuticals. So far, no American deaths have been linked to shoddy or fraudulent medications. But a surge in hazards discovered at home and abroad has cast new doubts on the safety of prescription and over-

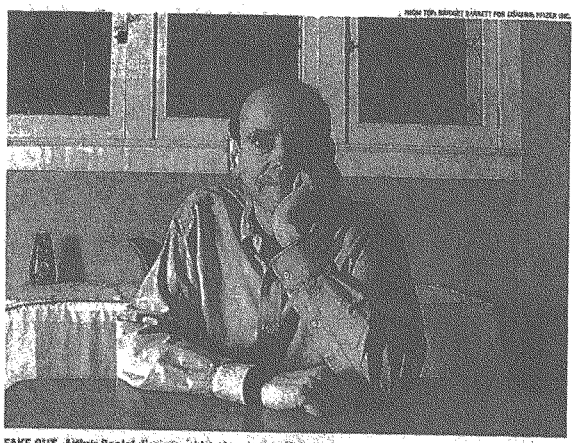
FROM TOP: JUPITER IMAGES; ANDY LYONS—GETTY IMAGES; SCOTT BARBOUR—GETTY IMAGES; ROMAINE JOHNSON FOR USNEWS

the-counter drugs, supplements, and other medical products. Americans "should be quite concerned," says Roger Williams, CEO of US Pharmacopeia, a private organization that creates the nation's official quality standards for drugs.

Americans still have the best pharmaceutical products in the world, says Williams. But the safety net is getting frayed. Recent problems with other goods imported from China, such as the melamine that tainted pet food and killed dozens of dogs and cats, and toothpaste made with diethylene glycol, have sparked worry that the pharmaceutical industry's rapid migration to manufacturing plants in China and other Asian countries is increasing the risk of similar problems with medicines.

Explosion of imports. In the past five years, Chinese pharmaceutical imports into the United States have more than doubled, to $698 million. Already, half of the aspirin used worldwide comes from China, as do 35 percent of the painkiller acetaminophen and almost all synthetic vitamin C. India's pharmaceutical imports into this country increased 2,400 percent, to $789 million, from 1996 to 2006, making it the fastest-growing drug importer. Last year, Indian firms won Food and Drug Administration approval to import more than 100 generic drugs, including a version of the anti-HIV drug Retrovir. India and China make about 20 percent of generic and over-the-counter drugs sold in the United States and at least half of the "active pharmaceutical ingredients" for pills made within the United States. "Ten years ago, the Chinese and Indian API market was nonexistent, and now they're dominant," says Lynne Jones Batshon, executive director of the Bulk Pharmaceuticals Task Force, a group of ingredient manufacturers. Price is a key driver of that shift, Batshon says, and complying with American regulatory requirements is expensive.

At the moment, consumers have no way of knowing where their drugs are produced or assembled, because there are no requirements for country-of-origin labeling of drugs. The counterfeit diabetes test strips were traced to a firm in Shanghai. And when at least 56 people died in Panama last fall after taking cough and allergy medicines, it was discovered that the drugs had been spiked with toxic diethylene glycol sold as harmless glycerin by a Chinese firm. Raw ingredients and finished products can move through a half-dozen countries before landing on a pharmacy shelf. Pharmacies buy from manufacturers or from wholesalers who are licensed by the states. "Our mantra is, the more often a product changes hands, the more likely a counterfeit can be introduced into the supply chain," says Rubie Mages, a former district attorney who is a director of global security for Pfizer, which makes Lipitor and Viagra, probably the world's most counterfeited drug.



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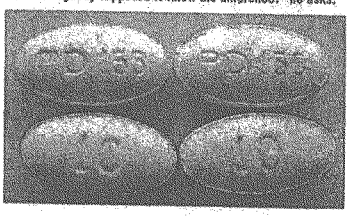


FAKE OUT. Arthur Socfof discovered by chance that Lipitor he had purchased from a local pharmacy was counterfeit. Below, the fake pills (left) are barely distinguishable from real ones. "How is anybody supposed to know the difference?" he asks.

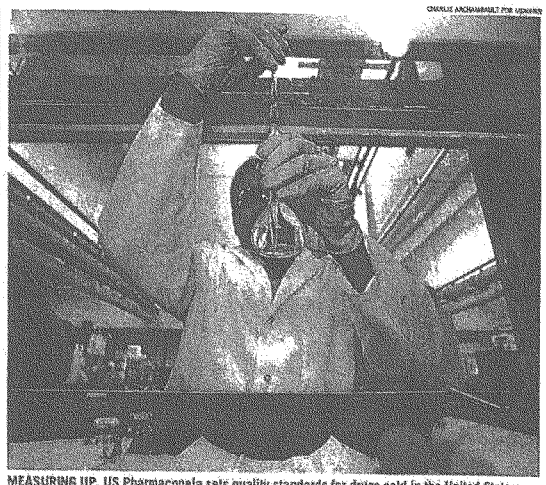
The FDA gained the authority to order tainted drugs off the market in 1938, after more than 100 people died in the States from taking medicine made with diethylene glycol. The federal regulatory system now requires manufacturers to test drugs for safety and efficacy before they are marketed, and also to quality-test the raw ingredients they use and the finished product. The FDA sends inspectors to domestic production facilities about every two years to make sure that they're in compliance; the inspections can take months. But the agency's enforcement division doesn't have the resources to inspect more than a tiny fraction of manufacturers overseas. Between 2,000 and 3,000 overseas pharmaceutical manufacturers that sell to the United States are registered with the FDA. Some of those have not been inspected in eight to 10 years, an FDA official told a congressional committee last month. And the suppliers of ingredients to those importers never get a look-over. "The FDA doesn't have the people who can go to these countries and inspect," says William Hubbard, a former associate com-

> One fraud was discovered because alert users of the product clued in the company selling it that they were getting odd results.

missioner for policy and planning at the agency. "The enforcement side has been cut drastically."

The public uproar over the pet deaths from melamine, as well as tainted toothpaste, got the government's attention. Congress has introduced several bills that would require country-of-origin labeling on pharmaceuticals, as well as fees on drug imports to pay for more inspections at the borders. An import-safety task force held hearings in Washington, D.C., last week, with the aim of preparing a report on possible solutions later this fall. And the Department of Health and Human Services is in the midst of negotiations with its Chinese counterpart over how to improve that country's food and drug safety programs. The top priority: the chemicals from which drugs are made. "We're very interested in oversight of the API industry in China," says Murray Lumpkin, deputy commissioner of the FDA's Office of International and Special Programs. In the past year, the standards-setting organization US Pharmacopeia opened offices in India and China, its first outside the United States. Some manufacturers in those countries have courted USP in an effort to prove they meet international standards.

People who rely on generic drugs may have to worry about more than the active ingredients, says Joe Graedon, a longtime champion of generics and coauthor of the 2006 book *Best Choices From the People's Pharmacy*. Since 2004, when the FDA fast-tracked the approval process for new generic drugs, more and more people have told him they've experienced side effects with a generic that they didn't have with the brand name, or the generic is failing to work at all. He wonders if differences in inactive ingredients or formulations could account for the treatment failures; when a company seeks FDA approval for a new generic, it must prove only that the active ingredient is the same. ConsumerLab.com is testing for differences between some generics and brand names; results are expected later this month.



CHARLIE ARCHAMBAULT FOR USNWR

MEASURING UP. US Pharmacopeia sets quality standards for drugs sold in the United States.

Spotting phonies. Even brand-name drugs you buy at the local pharmacy may pose dangers. Counterfeiting, says Hubbard, is extremely profitable and "a lot easier than selling narcotics. And you don't have to deal with a Colombian drug lord." The World Health Organization estimates that 10 percent of pharmaceuticals worldwide are counterfeit.

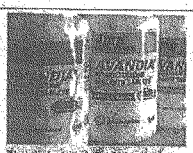
Sometimes, perceptive citizens must do their own detective work. Soclof, the Michigan allergist, had been taking half a pill of Lipitor daily to lower his cholesterol. In 2003, he picked up a refill and found that the pills wouldn't crack, no

The Other Safety Dilemma

The FDA may soon be better at monitoring drugs

Legitimate drugs, too, can pose unexpected dangers, as people who suffered heart problems after taking Vioxx or Avandia can attest. The number of serious adverse drug reactions reported to regulators in 2005 was nearly three times the 1998 number, according to a study published last month—and it grew four times faster than the number of outpatient prescriptions. And experts warn that the current system, which relies on health professionals and others to voluntarily report drug problems, flags only a fraction of the total.

But the tide may now be turning. A new law signed by President Bush in September substantially expands the Food and Drug Administration's power to take action after approval. The law directs the agency to routinely scan large private and government healthcare databases to identify drug safety problems. "This represents an entirely new approach," says Thomas J. Moore, a senior scientist at the Institute for Safe Medication Practices and the lead author on the adverse drug event study. "It would be a huge step forward if it can be done accurately." In addition, the agency gains authority to order drug manufacturers to make changes to labels—it's a negotiation now—and to fine them for false or misleading ads. Drug companies, for their part, will have to post clinical trial data for approved drugs and devices on the National Institutes of Health's clinical trials registry. Now, they can be selective. *–Michelle Andrews*



JUSTIN SULLIVAN—GETTY IMAGES

The diabetes drug Avandia has been linked to heart problems.

matter how hard he tried. "It used to break in half very easily," he says. He thought the sudden change was "really odd." A few days later he happened to see a newspaper article about counterfeit Lipitor being sold in pharmacies. Soclof called Pfizer, which manufactures Lipitor, and the FDA and was sent a FedEx envelope to return the suspect pills for testing. They were fake.

Like Soclof, customers are at a disadvantage when it comes to figuring out if the medications they get from their pharmacist or mail-order benefit plan are fakes. In many cases, counterfeiters imitate packaging of the legitimate company, as in the case of the fake OneTouch test strips. The fraud was discovered only because alert users clued in LifeScan Inc. of Milpitas, Calif., the company selling the strips, that they were getting odd results. At other times, counterfeiters mix real pills with fake (as in the case of the counterfeit Lipitor) or "uplabel," substituting 10-mg pills, say, for 40-mg ones.

> Supplement users concerned about quality and safety should be careful about herbals.

Experts in counterfeiting suggest that patients examine pills and packaging when they get a new prescription and note if the medicine tastes different, dissolves differently, or appears to have different effects. "We're big advocates of going back to the pharmacy" where the prescription was filled if something looks off, says Ilisa Bernstein, director of pharmacy affairs for the FDA. A pharmacist can help answer questions: Often a pharmacy will switch a patient from one generic to another, and the difference in the pills' appearance can spark needless worry. If in doubt, Bernstein says, take the medicine back to the pharmacy, or call the manufacturer.

For years, federal agencies have warned Internet shoppers of the risks of getting bogus or substandard medication. Yet the Internet drug trade is still booming. In May, the FDA announced that patients who had bought Xenical, a weight-loss drug, over the Internet received pills that looked identical to the Roche product but contained talc and starch. Other pills contained Meridia, a different weight-loss drug. In a June survey by MarkMonitor, a San Francisco-based firm that keeps tabs on online sales and marketing abuses, 38 percent of spam E-mail hawking Internet drugs came from China; 24 percent came from the Russian Federation; and just 2 percent came from sites actually in Canada, though many others claimed to be based there. An online pharmacy that falsely claimed to be in Canada sold the tainted drugs that killed Marcia Bergeron, the Vancouver Island woman. The MarkMonitor survey found that just four of the 3,160 pharmacies surveyed were certified by the National Association of Boards of Pharmacy (*www.nabp.net*), which vets online drugstores.

Suspect supplements. If there are troubling gaps in the regulation of imported pharmaceuticals, the oversight of nutritional supplements has yawning cavities. More than 150 million Americans take vitamin and mineral supplements regularly, but those tablets don't always contain all of the active ingredient claimed. In June, the FDA issued rules defining good manufacturing practices for supplements. But manufacturers still aren't required to prove dietary supplements are safe and effective by testing them before they enter the marketplace, as they are with prescription drugs.

Thus consumers tend to learn of safety and quality issues only after supplements are on the market. In August, for instance, the FDA warned people not to take red yeast rice supplements sold by Swanson Healthcare Products Inc. or Sunburst Biorganics because they contained lovastatin, a prescription drug used to treat high cholesterol. And in September, the agency recalled Axcil and Desirin, herbal supplements made by TWC Global of Mountain View, Calif., because the pills contained sildenafil, the active ingredient in Viagra. That drug can interact with nitrates taken for heart problems and may dangerously lower blood pressure.

In September, new ConsumerLab.com tests found that three of the 10 tested B-vitamin supplements had less folic acid than claimed. That may be because folic acid degrades if it's not stored properly, says President Tod Cooperman. Supplement purchasers concerned about quality and safety should be particularly careful about herbals, he says, because they are more likely to be of poor quality or contaminated. He suggests checking out independent laboratories that test supplements, including US Pharmacopeia (*www.usp.org*) and his company, ConsumerLab.com, which charges $29.95 a year for access to test data. Simplest of all, buy two different brands of multivitamins and switch daily. That way, he says, if one is subpar, at least the other may measure up. ●