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RESTORING FDA'S ABILITY TO KEEP AMERICA'S FAMILIES SAFE

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

ON

EXAMINING THE U.S. FOOD AND DRUG ADMINISTRATION, FOCUSING ON ITS ABILITY TO ENSURE THE SAFETY OF FOOD AND THE DRUG SUPPLY IN THE UNITED STATES

APRIL 24, 2008

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APRIL 24, 2008

ADDITIONAL MATERIAL

RESTORING FDA'S ABILITY TO KEEP AMERICA'S FAMILIES SAFE

THURSDAY, APRIL 24, 2008

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 9:36 a.m., in Room SD–106, Dirksen Senate Office Building, Hon. Edward M. Kennedy, chairman of the committee, presiding.

Present: Senators Kennedy, Dodd, Brown, Enzi, Alexander, Hatch, and Allard.

OPENING STATEMENT OF SENATOR KENNEDY

The CHAIRMAN. We'll come to order.

This is an enormously important hearing this morning, because the American people have an assumption that the food that they eat and the prescription drugs that they take—certainly with regard to prescription drugs are going to be safe and efficacious and that the food that they eat is going to be safe for themselves and for their children. That has been a general assumption over a very, very long period of time.

We've seen the evolution of changes, and rather dramatically, over the period of time, particularly with regard to food, as we find out that more and more food is imported. Most of the modalities that are set up for safety and security are home-grown, rather than being focused in terms of the international scene. We've also seen some disturbing trends, particularly the spinach. With regard to spinach and peanut butter and certain cereals, and with regards to prescription drugs, we've seen with the Heparin, the challenges that we've faced out there.

We see a FDA that is overstretched, in terms of its responsibilities, and under funded. We have some real, I think, some important responsibilities. We took note that the Appropriations Committee the other day—on the FDA—had a very, I think, interesting and important hearing in demonstrating the fact that the agency doesn't have the resources and funds. Many of us have been strong, strong advocates and supporters of an FDA that is going to be adequately funded, and brought into the 21st Century in terms of technology and in terms of scientific capability.

This is an important day today, and an important hearing. I'll put my full statement in the record, and we will ask Senator Enzi for any comments that he would like to make.

[The prepared statement of Senator Kennedy follows:]

PREPARED STATEMENT OF SENATOR KENNEDY

This hearing is about prevention: how do we prevent tragedies such as Heparin, or the continuing reports of unsafe spinach, peanut butter, breakfast cereal, and other foods?

These tragedies have common factors. All involve products regulated by FDA. All involve products that have killed or injured American consumers: more than 80 dead from Heparin, with hundreds more injured. Three killed by spinach last summer, and dozens sickened. All involve contaminated products, and failure by their manufacturers or growers to prevent them.

There are some important differences, however. Heparin involves one of the most highly regulated types of product—a prescription drug. FDA approved it before it could be marketed, and its manufacture is highly regulated, including a requirement to seek approval of changes to the process. Still, it illustrates gross inadequacy in this regulatory scheme. Its manufacturer didn't carefully scrutinize how it obtained the active ingredient, which is derived from pig intestines, in this case in China. FDA regulations apparently didn't require it to do so, and FDA never examined these sources itself.

The standard test for Heparin was unable to detect the contaminant. As a result, a tainted ingredient was brought into the United States and made into a deadly drug. The manufacturing process in high-tech plants ultimately proved meaningless to defeat the problem of raw materials shipped from grossly inadequate suppliers. Even the most up-to-date manufacturing processes won't ensure safety if manufacturers can't guarantee the ingredients aren't contaminated.

The Heparin contaminant is not naturally occurring. It may have been added intentionally, perhaps because of economic fraud.

It's unclear how FDA could have prevented this tragedy, given its current authorities and resources. An inspection of the Chinese supplier of the Heparin might have detected the intentional adulteration, if there had been open evidence of the crime in the plant. Because criminals tend to hide their activities, finding open evidence seems unlikely.

Practical solutions are available. Drug companies should be required to know more about the firms from which they obtain their ingredients, and audit them for ongoing compliance. Many reputable drug companies do so already.

Manufacturers must also use better tests of their own to detect impurities and contaminants. FDA obviously needs greater authority and significant additional resources to enforce these requirements, especially with respect to ingredients manufactured overseas. The mushrooming problem is clearly overwhelming the agency's current oversight.

By most accounts, the recent contaminants in food have not been intentional, but the solution is similar. Companies must be held accountable for preventing food-borne hazards. Many of the best companies already analyze hazards in food and adopt controls to avoid them. Preventive controls should be a standard requirement for every firm in the food industry, and FDA needs greater authorities and greater resources to oversee these responsibilities. Better sur-

veillance to detect food-borne illnesses and their causes will enable both FDA and the industry to respond more effectively when an outbreak occurs, and to focus on areas that have the most public health benefit.

It's the responsibility of manufacturers to build quality and safety into their products. They can use processes to ensure the quality and purity of ingredients, and FDA inspection can ensure that these processes are carefully and consistently implemented.

The immediate problem is FDA's lack of resources. As GAO reported yesterday, FDA inspects domestic drug establishments at close to the required rate of once every 2 years. But there is no similar requirement for inspecting foreign drug facilities, and the agency's performance reflects this disparity.

GAO estimates it will take FDA at least 13 years to inspect every foreign drug facility. Last year, it inspected only 30 of the more than 3,200 foreign drug plants, less than one out of every hundred. The agency's plan for the current fiscal year is to inspect 50 plants. GAO says it would cost 67 to 71 million dollars a year to inspect every foreign drug facility every other year, which is the rate required in the United States.

The agency's ability to inspect foreign food facilities is even worse. By one estimate, at the current rate, FDA will need 1,900 years to inspect every foreign food facility. These findings are very similar to the findings in the report of the FDA Science Board, which was a scathing indictment of the agency—scientifically, financially, and organizationally.

So we all have our work cut out for us. Fortunately, we have a distinguished group of witnesses today, and I thank them for joining us. I'm particularly grateful that Janet Woodcock of the FDA has agreed on short notice to discuss the Heparin situation. Thank you all, and I look forward to your insights and recommendations.

OPENING STATEMENT OF SENATOR ENZI

Senator ENZI.Good morning. As implied by the title of this hearing—"Restoring FDA's Ability to Keep America's Families Safe", we will be discussing a broad range of topics today. No doubt those topics will include food safety, import safety, and drug safety. However, this hearing is not aptly titled or focused. Rather than focus on all of the folks who could assist with the emerging world market, we are instead only focusing on what the Food and Drug Administration (FDA) can do. That's a limited view of what can and should be done. The complex nature of the situation requires all of the global partners—regulators, importers, manufacturers, academia—and other stakeholders to come together to propose meaningful, collaborative solutions.

Let's just admit the basic fact: *We cannot inspect our way to safety*. While it is unfortunate that the FDA was unable to inspect a particular heparin manufacturing facility in China, an inspection would not have resulted in a safer heparin product. The potential contamination happened before the items reached the manufacturing facility. Of course, that's the specifics of one situation.

As you can see on the chart behind me, there are dozens of facilities around the world that supply us with drugs and active pharmaceutical ingredients. The true extent of foreign sources of our

food and drug supply can sometimes be shocking. We need that reality check. That access is necessary to meet the demands of American consumers. The FDA must do all it can to ensure that these products are safe to consume. However, the reality of the global economy is that testing every food and drug product from outside the United States is not currently possible, nor will it ever be.

Even with the increased number of inspectors, the FDA only inspects about 1 percent of all imported food. While that percentage could be higher, inspections cannot and should not be the only tool in the FDA toolbox to deal with import safety issues. That's why I am encouraged by two recent FDA actions.

First, the FDA reported that they would be opening three new offices in China by October. Given the wide range of imported products from China, it is always good to have someone on the ground to assess the current situation, build relationships, and possibly head off an international incident.

Second, I support the efforts made by the FDA's Food Protection Plan with its focus on prevention, intervention and response. I would like to use it as the basis for the food safety legislation that the HELP Committee will move in the coming months.

I often remind my staff: If it is worth reacting to, it is worth over-reacting to. In our future discussions on import safety, we must remember that. Just last year, we gave FDA broad new authorities to deal with a whole host of drug safety issues. Rather than jump to quickly amend those new provisions, we should give FDA the time to fully utilize those new authorities and evaluate their effectiveness.

However, there are some areas on which we could quickly reach agreement on the need for improvement. That's the 80 percent of this issue. If we focus on that 80 percent and work together on the substance of these issues that we already agree on, we will be able to make progress and get something done quickly. If not, we will find ourselves stuck on the 20 percent that separates us and walk away from these discussions empty handed, with nothing to show for our efforts.

That is why I hope we will not be distracted by extraneous policies and instead continue to focus on common ground. Like it or not, our window of opportunity for swift action will soon be closing. We have two options—we can focus on what we can get done using my 80 percent rule, or, we can over-reach and under achieve.

That is why I urge all my colleagues and our staffs to stay focused on what is possible to get done now—so that we get something done—now!

I look forward to the testimony today, and I thank the Chairman.

The CHAIRMAN. Thank you very much.

We'll call for brief comments, if there are, Senator Dodd.

STATEMENT OF SENATOR DODD

Senator DODD. Just very briefly, Mr. Chairman, and thank you, immensely, for holding this hearing. It is tremendously important subject matter and you said it well in your opening statement—this is an assumption we all make, all of us did this morning when we got up and had breakfast with our families—all of the assumptions

we made were about how safe the products we consume are. We're learning, painfully, that that's not the case, in so many instances.

This hearing to examine what we can do to increase and improve food and drug safety makes a tremendous amount of sense.

The only thing I'd want to add at all to this—and we're going to in fact have a hearing in our own subcommittee next month, that will deal with food allergy issues and the truth in advertising here is that I am the father of a 6-year-old, with very profound and severe food allergies, who has been in anaphylactic shock four times already by the age of 6. Three million children are like my daughter, Grace, who runs the risk every single day of consuming a product, without those Epi pens available, that could cause her to lose her life.

I'm hopeful that in the process here we can address food allergies, particularly in schools. A lot of States—12 States are already working on food allergy management issues at schools. Food labeling is a challenging issue for a parent, trying to read every label, as I do for everything she eats, to make sure there's not contamination with an allergen. She's subjected to airborne problems—not just consumption, internally. My hope would be, in the process of moving forward on food and drug safety issues, we can talk about how food allergies could also be a part of this.

Thank you.

The CHAIRMAN. Thank you very much.

I see my friends Senator Hatch and Senator Allard wanted to say a brief word, I'll ask Senator Brown if he would say a word, and we'll get started.

STATEMENT OF SENATOR ALLARD

Senator ALLARD. Well, thank you, Mr. Chairman. I don't have any prepared statement, but I'm looking forward to the testimony. I have a lot of interest in Food and Drug Administration for a number of reasons: because I am a veterinarian, and also because we have, I think, some conflicts of jurisdiction we have to keep in mind, between the Ag Department (in terms of food inspection) and FDA. Also, we must make sure that we don't have regulatory duplication, while still ensuring a safe food supply.

This country has the safest food supply, the best and safest pharmaceuticals—which have also been developed here in this country where the inspection and the quality control starts right at the origination point. When we import foods, we don't have the same oversight over quality and so we have to figure out what the proper balance is between trade and regulation to maintain a safe and varied food supply for Americans.

Thank you.

STATEMENT OF SENATOR BROWN

Senator BROWN. Thank you, Mr. Chairman. Thank you for holding this hearing.

When we import from overseas, we're to some extent, importing the health and safety standards of the countries we trade with. Appropriate story, a woman from Ravenna, OH told us, 73 years old, recently undergoing dental work, had to have a dental bridge re-

moved. She'd read several stories about led in toys, she decided to have the bridge in her mouth tested for lead, and learned that the bridge contained 160 parts per million of lead.

Those kinds of things are happening too often. It's all of these issues of food and toys and contaminants and vitamins and all of that, it's a trade—and prescription drugs—it's a trade issue. Think of the toys and the lead and American companies outsourcing jobs to China, and then subcontracting with Chinese companies and demanding that they cut the costs of their production. That's why we have lead paint in toys, more than any other reason.

It's a deregulation issue, that we have continued in the last few years to weaken rules and regulations protecting public health and public safety. It's a food and labeling issue, as Senator Dodd pointed out, and it's an inspection issue, as this government continues to cut funding for fruits and vegetables coming across the Mexican border, for consumer product safety coming from China, from a whole host of issues that contaminate our vitamins and our food and our dog food, and a whole host of issues.

That's why this hearing is so important.

Thank you, Mr. Chairman.

[The prepared statement of Senator Brown follows:]

PREPARED STATEMENT OF SENATOR BROWN

A lot of you are familiar with the issues we're going to hear about today. They've been in the news again and again—*e. coli* in spinach and salad mixes, salmonella in pet food, the list goes on.

We're also hearing about contaminated pharmaceuticals, most recently, Heparin.

We're going to hear today about FDA's ability to deal with these threats.

But we are really talking about much more.

We're talking about how we respond as a nation to a changing world. We are more interdependent than ever before in this global economy. When we import from overseas, we are to some extent importing the health and other standards of those countries as well. We potentially affect—and are affected by—every one of our trading partners.

But we haven't recognized this new reality.

We have kept our heads in the sand and followed a path of neglect for far too long. And the results are all too obvious and the impact can be felt all across America and in my State of Ohio.

Adulterated Heparin from China is suspected in the deaths of 7 residents in Toledo, OH. And recently, I've heard from constituents in my State about dental crowns imported from China that contain lead. A woman from Ravenna, OH called my office this week to tell her story.

She is 73-years-old and recently, after undergoing dental work, had to have a dental bridge removed. At that time, she had read several stories about lead in toys. She decided to have the bridge tested for lead. She learned that the bridge contained 160 parts per million of lead.

As Mark Feldman, President of the American Dental Association points out, lead should not be in any FDA-approved dental mate-

rials. The American Academy of Pediatrics contends that there is no 'safe' level of lead exposure.

This is just one story that exemplifies the problems we are facing with the FDA.

We are challenged not only with contaminated pharmaceuticals that have not undergone sufficient inspection, but insufficient regulation of imported medical and dental devices, too.

How we choose to manage the challenges of globalization will determine our future. We can choose to continue on our path of neglect or we can choose to take action.

The Food and Drug Administration has been relying on an import plan developed in the 1970's when imports were low. Today, trillions of dollars of goods are imported from hundreds of thousands of importers.

FDA can not even count them.

Thousands of overseas food and drug manufacturers are shipping to the United States, yet FDA has little data about what happens in overseas facilities and supply chains.

FDA does not have the resources to inspect them. FDA did not inspect the Chinese plant that supplied the contaminant linked to 81 deaths among Heparin users in the United States.

The Administration's new import plan has some ideas for improving the situation. But according to the GAO, the plan doesn't fully address the problems in the Foreign Drug Inspection Program. The GAO estimates that in order for FDA to begin full inspections of foreign plants, it needs an additional $56 million dollars next year.

It also needs at least $15 million a year to bring inspections of Chinese drug plants up to domestic standards—inspecting every 2 years. It needs 27 years to inspect every foreign medical device plant, 13 years to inspect every foreign drug plant, and 1,900 years to inspect every foreign food plant at the current rate that it's going.

But the President's budget doesn't provide the money we need to hire more inspectors.

And what are we going to do in the meantime?

Every American is going to be worried the next time he or she undergoes a medical or dental procedure or is required to take medication for a health problem.

We have the most advanced health system in the world. There is no excuse for a country with our resources to be falling victim to such negligence.

It's time to get serious now.

Our future and the health of our country depends on it.

Thank you.

The CHAIRMAN. Senator Hatch, is there anything you'd like to add? Or we'll move on.

Thank you very much.

Senator HATCH. Thank you very much, Mr. Chairman.

The CHAIRMAN. Well, you've been a strong, strong advocate for the agency over many, many years, so we always welcome your involvement and participation in the hearing.

We'll ask Dr. Woodcock, if she'd be kind enough to come forward—she's the head of the FDA's Center for Drugs, she's accom-

panied by Deb Autor, who is the Drug Compliance Director, and Moheb Nasr, who's the Drug Quality Director.

Janet Woodcock is one of those extraordinary public servants that has been with the agency over 20 years—how many years has it been?

Dr. WOODCOCK. Twenty.

The CHAIRMAN. Twenty years, and has been a enormously gifted and talented scientist and researcher and public servant. She had incredible opportunities to go to the private sector or the nonprofit sector, and has had a very comfortable, productive and useful life. She's stayed at the FDA and been an enormously valuable asset to that agency and to the protection of the Nation's food and drug supplies, so we're enormously grateful for your service, and for your presence here today.

Thank you very much, Doctor.

STATEMENT OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD; ACCOMPANIED BY MOHEB N. NASR, DRUG QUALITY DIRECTOR AND DEBORAH M. AUTOR, DRUG COMPLIANCE DIRECTOR

Dr. WOODCOCK. Thank you.

Mr. Chairman, and distinguished Senators, I'm Janet Woodcock, Director of the Center for Drugs at FDA, and I thank you for the opportunity to discuss the important issue of the safety of the drug supply in the United States, and the example of the Heparin contamination that we've been experiencing recently.

The U.S. drug supply has long been one of the world's safest. This reliable quality was really the result of a framework that was put in place by Congress and implemented by the FDA, that controlled and regulated the manufacturing and the movement of pharmaceuticals in the United States.

In contrast, in many parts of the world, even today, consumers purchasing a medicine may only have a 50 percent chance of getting a product that is what it says on the label. In some countries, that's the level of counterfeiting that currently exists.

In this country, we may have forgotten that the drug supply here was once dangerous, and that great vigilance is required to maintain its safety.

Over the past several decades, dramatic changes in the pharmaceutical manufacturing environment have occurred, that have impacted on this potential safety. First, many more Americans are taking many more medicines. The number of pharmaceutical products on the market has grown dramatically, and so has the number of people, and the number of medicines that people take. Of course, this is good news, and not-so-good news in some cases.

The risks posed by quality problems, and the complexity of regulating pharmaceutical quality has considerably increased as a result of this.

Second, the sites of production of pharmaceuticals have dramatically changed from what was the case in the seventies. FDA has traditionally been configured, as an agency, to regulate a domestic industry, using a field force that's located in District Offices around the United States to perform inspections.

Over the past 15 years, the majority of active pharmaceutical ingredient manufacture—in other words, the active drug product—has moved offshore. That production is in other places around the world. Increasingly, the final drug products are also made in various countries around the world, and then those finished products are imported into the United States.

The FDA of the last century is not configured to regulate this century's globalized pharmaceutical manufacturing industry.

Third, the complexity of modern manufacturing arrangements requires more sophisticated management methods on the part of regulators. It used to be that we had, as I said, there was a single manufacturing plant—often somewhere in the United States—that would receive their ingredients from other parts of the United States, it would all be assembled there, within that District, and then made into a finished product.

Currently, some generic drug applications submitted to FDA may cite 15 different facilities in the application, and these facilities may be located anywhere around the world. That's one application. We, right now, are approving around 400 generic drugs each year in the United States.

As has been seen in the Heparin incident, intermediates and products can now move in the globalized world through a complicated web of distribution. They may originate in one continent, be shipped to another continent, to be made into an active pharmaceutical ingredient, and then be shipped to yet another continent to be made into a finished drug product, and then be imported into the United States.

Contaminated Heparin batches ended up in a large number of different products all around the world. More sophisticated IT and informatic approaches are required on the part of regulators in this globalized world to monitor the supply chain. The supply chain is not manageable by our traditional methods.

Finally, in the face of all of this growth and change, FDA's inspectional resources for pharmaceuticals have actually diminished in real terms. While the number of registered establishments have quadrupled, at least, over 25 years, the number of good manufacturing practice inspections of pharmaceuticals that FDA is able to conduct has dropped significantly, in the same time. Inspectional resources have actually dropped, while responsibilities have soared.

But this situation can be addressed, and that's what I'm here today to say. The remedy is actually very straightforward. This approach is taken in other manufacturing sectors. All parties throughout the supply chain—from the production of the API and the ingredients, through brokers, through distributors, through importers, to finished product manufacturers—must be held responsible. They are the ones who must be held responsible for assuring the quality and integrity of the products they produce.

As was just said, the FDA or any other worldwide regulator cannot test quality into products, and we cannot inspect quality into products. What we must do—the FDA must have the tools to hold all of these parties accountable. We need to be able to find them, know who they are, and have the authority and resources to hold them accountable for quality.

These tools include resources for inspections, for modern IT systems, for laboratories and review science, because science is the way we will advance, and move forward, and actually overcome these problems in the future, and also education and outreach, because we are going—as we have global players, they need to be educated about the quality standards, including regulators in other parts of the world, we need to assist them.

Also, we need new sets of authorities that recognize the global environment we are in, and give us the tools to hold all of these parties accountable.

If these improvements occur, I think we can continue to be assured that the U.S. drug supply will be one of the safest in the world.

Thank you.

The CHAIRMAN. Thank you very much and for your suggestions and recommendations.

Let me ask you just about Heparin, because that's been the principal concern.

You've identified lots from 2006 of bulk Heparin active ingredient that included the contaminant, and Heparin made with those lots would have reached patients in 2007?

Dr. WOODCOCK. Yes.

The CHAIRMAN. Have you verified there were no Heparin lots earlier than 2006 that included the contaminant?

Dr. WOODCOCK. No, in fact, we have reports of lots that may have been contaminated earlier, but these we have not been able to confirm—we wish to confirm these in our own laboratories.

What we did was put testing methods up on the web, and we asked manufacturers and regulatory authorities around the world to do the tests, and we provided resources from Dr. Nasr's shop to help people with the testing and from Deb's shop—the Office of Compliance—to receive all of this information, and we've been compiling this information.

It appears that the bulk of the contaminant occurred in 2006, because some manufacturers have gone back and tested many lots prior to that, and have not seen it. However, we do have some reports of sporadic lots going back further, that's correct. But we have not verified that ourselves.

The CHAIRMAN. Do you know what the risks of the contaminant are, both the short-term and long-term, and what should be done to assess those risks?

Dr. WOODCOCK. We published a paper—we published online last night in the New England Journal of Medicine—with authors from the FDA, as well as people from MIT and Virginia Tech and others, establishing a potential link between the acute reactions to this product—the hypotension and other adverse, serious, adverse events that were observed—in a biological mechanism. So, we have some understanding of that.

We know that the vast majority of people who were exposed to this did not suffer any acute reaction. We are proceeding now, looking at whether there might be any longer-term consequences to exposure of this.

There was a product in Europe, that was approved and on the market, that was very similar to this contaminant. It was taken off

the market in Europe a number of years ago for side effects, but it was a marketed product in Europe. We are going to follow up on this issue.

Senator HATCH. Mr. Chairman.

The CHAIRMAN. Yes.

Senator HATCH. I have to leave, could I just ask one question? I don't mean to interrupt you, but——

The CHAIRMAN. Go ahead.

Senator HATCH. Have you done an analysis of how much you would like to have to rectify the situation at FDA? To strengthen FDA? How much would it cost? Just so we know up here?

Dr. WOODCOCK. For the pharmaceutical part of this?

Senator HATCH. For what you think has to be done to protect the American people in all of these areas?

Dr. WOODCOCK. There are different parts of pharmaceutical regulation that need to be strengthened, one part is authorities, and one part is the inspection and testing and those resources, as I said. I think that would—I don't have a number right now, and I'm being honest—be a substantial increase to our inspectional resources, they are very inadequate right now, as has been publicized.

We really do not inspect most of the facilities overseas, very much at all.

Senator HATCH. Mr. Chairman, we treat this agency pretty shabbily, it seems to me, compared to what it really does for this country, and for the world at large. I'm just hoping that we can all get together and maybe find some way of giving them the resources that they need to do what we all know needs to be done.

The CHAIRMAN. Why don't we——

Senator HATCH. Sorry to interrupt you, I do apologize, I'm grateful for your graciousness.

The CHAIRMAN [continuing]. Inquire of you, and give you time to respond. We'll work with Senator Hatch and other members of the committee and be somewhat specific and give you an opportunity to respond. We know it's the budget item, but we're also entitled as members to inquire of you for a professional opinion.

Senator HATCH. We can fight for you, too. I just want you to know how much we appreciate you.

Senator ALLARD. Mr. Chairman, if I might interject. I think it would be helpful—Dr. Woodcock, you indicated a number of areas where you thought you needed additional resources; I think it would be helpful for you to break out your costs in each one of those areas and prioritize those. I'm guessing that laboratory enhancement is your No. 1 priority. This would be helpful so that if we don't have enough money, at least we can focus on those areas most in need.

Dr. WOODCOCK. Right, well, I testified before the Agriculture Appropriations Committee in the House a number of weeks ago, and our No. 1 priority is to develop—to have an inventory of every establishment in the world that is importing into the United States so that we can verify when these products come across the border that they should be allowed in the United States. That is our No. 1 priority. We've developed a business plan, and costed out how

much that would be. We also need the inspectional resources as well as the laboratory and testing resources.

The CHAIRMAN. OK. We'll follow up——

Dr. WOODCOCK. We will get back to you.

The CHAIRMAN. In final, on the issue of the Heparin, what would you advise a patient who needs Heparin today? What advice would you give him?

Dr. WOODCOCK. Thanks to the efforts of Dr. Nasr and his colleagues and the Office of Compliance in Cedar, and numerous other people across the agency, and actually researchers in universities, we believe that the Heparin supply in the United States right now, is safe. It is all tested, we do not have any Heparin product in the United States going into patients on the market right now that contains this contaminant.

People can feel assured that if they need Heparin for a procedure, or they're going to dialysis, the Heparin they will receive does not contain this contaminant. We have instituted testing at every manufacturer, and we're stopping products at the border to make sure it doesn't get in unless it has been tested, or will be tested. We're confident that the Heparin supply right now, in the United States, is safe.

The CHAIRMAN. You suggested that we and Germany have seen adverse events from the contaminated Heparin, because Heparin is administered in what they call a "bolus" dose in these countries, and my understanding is that the bolus dosing is standard international medical practice for acute situations where there's a blood clot. Could you clarify?

Dr. WOODCOCK. Sure. We do not completely understand why some people got a reaction, and others didn't. The paper we've published on the biological link is the first step in trying to develop a medical, scientific understanding of why some people got side effects, and others didn't, when many people were exposed.

The contaminant is present worldwide, and yet adverse events, yes, only were observed in clusters, in Germany, and in the United States.

Some regulatory agencies, such as France, have recommended that bolus dosing not occur with certain products right now, because of the fear that that could trigger an adverse event. We can't give you, today, an explanation about why some people got this event, and some others—the bolus dosing appears to be associated, or rapid intravenous dosing.

Some countries do give a bolus, but they give it over a longer period of time, rather than an inner—just rapidly injecting it into the patient. Based on our scientific findings that were published yesterday, that could trigger a reaction, if you gave it in a very quickly, quick bolus, rather than a slow bolus.

When we first had this problem in February, we advised the health community in the United States to move to a slower administration of Heparin.

The CHAIRMAN. Just a final question—there will be a question about whether this contaminant slipped into the product. Was it accidental? Is it so pronounced that one would have to conclude it's purposeful? I know that's probably a loaded question, I don't know whether you want to take a crack at it, but it does seem to me that

we're talking about a volume of contaminant to be very difficult to assume that it was just some mistake that happened along the pathway. If it was purposefully used in this product, that raises enormously serious and significant foreign policy issues.

Dr. WOODCOCK. We have no proof or evidence about how this got into the product. However, some lots had an extremely high level of contamination, and we know that this was a synthetic product, it was not a natural product that accidentally contaminated. How it got in there, whether there was a mix-up, or whether it was deliberately added, we cannot tell you, right now, definitely.

Dr. Nasr may want to comment on the production, and how that could have occurred.

Dr. NASR. Good morning, Moheb Nasr.

Mr. Chairman, based on our scientific investigation, I can summarize it in the following way: that contaminant has been present at a smaller amount for a period of time. However, in all seven, we have seen an elevated amount of this contaminant in batches that were associated with the adverse event.

The CHAIRMAN. Well, give that to me in——

[Laughter.]

Dr. WOODCOCK. Right. What we saw as we looked at a time course of this problem, and we looked back, because we require manufacturer, and they hold retention samples of the APIs that went into the finished product, so we had them go back and do retrospective testing, and we saw a small amount start entering the supply chain in 2006, and then get on the market, and then a larger amount.

Some of the latest batches that were associated with adverse events had up to, what, 20 percent? Is that fair?

Dr. NASR. Up to 27 percent.

Dr. WOODCOCK. Of the finished product?

Dr. NASR. Yes.

Dr. WOODCOCK. Of the finished product, so almost a third of the Heparin product was this contaminant. Your point is, it seems—it's sort of strains credulity—how that could have gotten in there accidentally.

The CHAIRMAN. You've made my point very clearly. Particularly, as I understand this is a product that comes from China, am I correct?

Dr. WOODCOCK. There's different sourcing. China sources about 80 percent, and we had a meeting of the International Regulators last week, including the Chinese regulators, and all of the contaminated lots that have been found—which have been a large number—have all originated from China.

The CHAIRMAN. My time is well over.

Please, Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

We had a great series of hearings earlier on food safety, after the spinach and the peanut butter incidents, and we were very pleased to find out about the cooperation between FDA, CDC, USDA and their ability to take very few cases across the United States and figure out a problem, and pinpoint where it came from.

You mentioned that you just published the results in a journal, or online last night. What other indications would there have been

earlier? What are the steps that are taken from suspicion, to proving, to solving?

Dr. WOODCOCK. Right. This episode, this outbreak was detected by the CDC. Originally, there were reports to Departments of Public Health who reported to the CDC about problems after dialysis patients had received dialysis, or initiating dialysis.

The CDC investigated this originally, and of course, that's a very complicated situation, where you have a dialysis machine, you have tubing, you have different drug problems—all of which have been associated with different adverse events in the past.

We collaborated with the CDC in sorting this out, as well as the manufacturer, Baxter. The real epidemic was identified in January, and by March we had identified the contaminant, put up tests to test the Heparin supply, and now we've published a paper on the biological link. We accomplished these activities in a very short period of time.

Senator ENZI. I'll ask some additional, more technical questions on that later, but can you tell me about the International Rapid Alert Notification System? It sounds like the FDA relied heavily on that system to share the results of the inspections and the testing during this incident. How does that work?

Dr. WOODCOCK. Yeah, I'll ask Ms. Autor to answer that.

Ms. AUTOR. There are actually a couple of different systems internationally, which helped us with this incident. One is that we have an international alert system where we learn about the most serious recalls going on in other countries. That helped us, for example, to learn about the German incident.

The other thing that we did is, when we posted our test methodology for the contaminant on our Web site, we also created a hotline—both a phone number and an e-mail address. We received approximately 83 contacts from regulators in industry around the world, which helped to tell us where the contaminant was being found, and also helped us to answer the technical questions for the companies and the regulators who are trying to understand how to test for the contaminant and whether they had contaminated Heparin.

Senator ENZI. Thank you, and again, I'll ask some more in writing, on the timeline for how that happens.

I do think that it's good news that China is beginning to conduct export testing on Heparin. It's my understanding the factory that made the Heparin considered itself a chemical plant, not a drug plant. It wasn't registered with the Chinese government. How can we be sure that China's export testing is good enough to ensure that factories producing Heparin have that product tested?

Dr. WOODCOCK. Let me say, and then maybe Ms. Autor may want to add to this—we are also requiring manufacturers to do very extensive testing of the Heparin APIs when they receive them. There is more sophisticated testing available in the United States that will identify this contaminant to an extremely low level of presence. So we can be sure that it will be removed.

In our International Regulator's meeting, we met with the U.S. pharmacopoeia. They've participated in this meeting, as well as the European pharmacopoeia. They will rapidly be incorporating tests into the pharmacopoeial standards. That would mean that all of

those countries in Europe and the United States, any Heparin moving around in commerce would have to meet those standards, and pass those tests.

As far as the China testing——

Ms. AUTOR. Let me add to that—I do think it's a very positive step that China is testing Heparin for export. However, China does not regulate, as pharmaceutical companies that say they are chemical manufacturers, and China also does not have heavy regulation of products that are intended for export only. At the end of the day, I do not believe we can rely on China as the only protection of American consumers, and the American drug supply. They are taking steps, they are improving their regulation, but again, it's incumbent upon the manufacturers to ensure that the products they're getting have the adequate quality and integrity.

Senator ENZI. So, once it's found, then testing moves, in effect, to the ultimate company, the final company. Only after there's some kind of a difficulty like this, I assume. Nobody was testing the Heparin beforehand?

Dr. WOODCOCK. Right. There were what are called pharmacopoeial standards, and other standards for Heparin that were in place, and this is what was very interesting about this incident. This contaminant was chemically modified to enable it to—it mimicked Heparin in the existing tests that we had. It was not detected by the manufacturers when they got the contaminated batches of raw Heparin, of API Heparin. Because when they did the normal tests, that passed—even when it had 30 percent of something that wasn't Heparin in it.

It took more sophisticated modern tests to determine this. Actually, our analysts had this in their laboratory, some of them, for several weeks. It took them that long, with all their analytical instruments, to actually figure out what this was. Because it's very similar to Heparin.

Senator ENZI. Thank you. I have a whole bunch more questions, but I'll submit those in writing, since my time is expired.

The CHAIRMAN. Senator Brown.

Senator BROWN. Thank you, Mr. Chairman.

I'm, of course, troubled, Dr. Woodcock, by the uncertainty of accuracy of labels, depending in part on where the ingredients come from.

I want to talk about the whole issue of how we do inspections of ingredients coming from China. I understand FDA plans to open three offices in China, and will assign 13 employees to staff these offices—does that get us very far?

Dr. WOODCOCK. What that does is provide a—as someone said already—a presence on the ground in China. It doesn't get us out there doing all of the inspections, potentially, that we need to do, but we'll have people in China who know what is going on in China, and that is a very important step.

I'll have Deb talk about the inspectional issues.

Ms. AUTOR. Having the offices in China is a good start. It allows us to do a lot of capacity-building, it allows us to do some inspections, and as Dr. Woodcock said, it allows us to have a presence on the ground to observe conditions.

Ultimately, our resources and our ability to inspect drug manufacturers in China are very limited. The GAO, I think, has said that internationally, at the rate we're going, we'll get to every facility every 13 years, or in China, every facility every 40 yeas. While it's a start, it won't create——

Senator BROWN. Well, what does that mean? Based on having 3 offices and 13 employees? Or based on what we could be doing if you had the right kind of appropriation and the right direction?

Ms. AUTOR. Based on our current inspectional rate internationally, and specifically in China—that's our ability to cover the Chinese inventory. Having the offices there will allow us to do somewhat more inspections, but we currently have over 800 Chinese drug manufacturing facilities. Having 13 people on the ground in China, responsible for covering all FDA-regulated products, will not allow us to cover a significant proportion of those.

Senator BROWN. How long does it take to inspect a typical foreign drug manufacturing plant?

Ms. AUTOR. Our typical foreign inspections are about a week.

Senator BROWN. With how many inspectors?

Ms. AUTOR. Usually two.

Senator BROWN. Two? These inspectors are trained—what is their training?

Ms. AUTOR. It varies somewhat, but we have special training on how to conduct pharmaceutical inspections—either, they usually are trained FDA inspectors and then they would have some extra training on pharmaceutical inspections, and at time we will bring review chemists, or others who have particular expertise in the product, along on inspections so they can help. They range from people with a Bachelor's Degree in Science, to Ph.D.s.

Senator BROWN. Why, with all of the stories there's a bit of an exaggeration, but a monthly, maybe weekly, report of some contaminated or unsafe or toxic toy, food substance, vitamin, pharmaceutical, coming from China to this country—why such a modest approach? Is it all about budget to send 13 employees and 3 offices to a country of 1.2 billion people?

Dr. WOODCOCK. As I pointed out in my introductory remarks, FDA was staffed and configured to regulate a domestic industry. Times have changed—we haven't changed—we've shrunk. Our inspectional capacity has shrunk.

There's several issues, though. One is it's—without some special foreign inspector, I think it's difficult to get our people to go there, and we can't force people to go and do foreign inspections. We need to recognize and probably establish an inspectorate, that will do foreign inspections, so that that's the expectation.

Maybe people would like to rotate through that, and not do that for the rest of their lives, however, that's one thing that we don't have. That's an example of—we need to change our approach to match the current reality of where products are produced.

Senator BROWN. Does a domestic inspection take any longer time or shorter time than an inspection in China?

Ms. AUTOR. They tend to average a slightly longer time for a variety of reasons.

Senator BROWN. Could you give me one or two of the most prominent reasons?

Ms. AUTOR. I think in part there is less pressure to get them done, they're not under such a tight itinerary, and so they're able to go at a slower pace. The foreign inspectors, I'm told, are working pretty much around the clock when they're there, because they have a short time to get all of their work done. That's less of an issue domestically.

Senator BROWN. Let me ask a theoretical question that's troubled me since—well frankly, since the passage of the North American Free Trade Agreement and what's happened with the amount of—and I know this is partly agriculture, partly FDA—the amount of food that has come across the border. The good news is that we eat more fruits and vegetables, in part because we—of all times of the year, because we import a lot of fruits, fresh fruits and vegetables.

My recollection is that in pre-NAFTA days, we inspected about 8 percent of fruits and vegetables coming into the United States. Today, at least, from South of the Border, today that percentage is one—about one-eighth, one-tenth, one-fifth, that's something significantly less.

The theoretical question is—understanding we'll never inspect 100 percent, as Senator Enzi pointed out—is there sort of a mathematical, statistical analysis, that if you inspect X percent, that it really does guarantee—not guarantee, but suggest or promise with some amount of certainty, that something is safe. Is it 3 percent or 8 percent or 20 percent? What gets you—part of the disincentives for those who might adulterate food, or be less careful, but partly sort of a statistical issue—can you speak to that?

Dr. WOODCOCK. Not very well, because I'm not an expert in the food area.

I will tell you that—especially, I would think, for food—you can't inspect quality in, because you can't see microbes and you can't see pesticide contamination by inspecting.

In may be—and that's where research is needed—with better probes that you could use instantly——

Senator BROWN. We have some detection equipment now that can do that pretty quickly, in come cases, is my understanding.

Dr. WOODCOCK. They're limited.

Senator BROWN. OK, limited, okay.

Dr. WOODCOCK. Very limited.

Inspection as a deterrent, at the border, has to be seen as one part of a whole—one component of a quality system, and the real goad, I think, for foods, as well as pharmaceuticals, has to be to hold the producers accountable, to have very good mechanisms, to hold them accountable, say, for good agricultural practices, or in the case of drugs, for good manufacturing practices. We make sure that they do the right things, because we can not be the quality control unit for the world. We are never going to have enough resources to do that.

Senator BROWN. My time is expired, thank you, Mr. Chairman.

The CHAIRMAN. OK.

Senator Allard.

Senator ALLARD. Thank you, Mr. Chairman.

It seems to me that the surveillance procedures that were put in place were working. Through the reporting to the CDC lab, we no-

ticed an aberration in the occurrences of reactions, which raised an alert. That aspect did work; would you agree with that?

Dr. WOODCOCK. Yes, that did work, and we were able to rapidly respond, once it was identified there was an outbreak, and it was then linked to Heparin.

Senator ALLARD. Yes. I'd like to have a clarification of your testimony earlier—you said that Germany and the United States used a bolus treatment for Heparin; is that correct?

Dr. WOODCOCK. Yes.

Senator ALLARD. And that you think that negative reactions occurred in this country and Germany, as opposed to other countries, because the contaminant through the bolus treatment was causing the reaction. It is not that previous reactions weren't reported, right?

Dr. WOODCOCK. Well, the problem with Heparin and all of these incenses, is that there is a background rate of people getting hypotensive—low blood pressure—who are on dialysis or who are undergoing cardiac procedures.

First of all, you may not recognize that, it's unusual, because it happens anyway. Then you may have trouble linking it to Heparin, because there are multiple other things going on.

Senator ALLARD. I understand that.

Dr. WOODCOCK. However, here we saw clusters, where multiple patients in a dialysis center got the same reaction. That was seen in Germany, as well as the United States.

We can't guarantee, I'm sorry, we can't guarantee that this contaminant caused it. We have published a biological link. We know, as Dr. Nasr said, that lots with high concentrations were associated with some of these reactions.

Senator ALLARD. But other countries have taken it off the market because of side effects of some type?

Dr. WOODCOCK. They have not seen side effects, but Heparin should not be contaminated with other compounds.

Senator ALLARD. No.

Heparin is a relatively small protein, I would suspect, compared to Chondroitin?

Dr. WOODCOCK. It's a large carbohydrate similar to——

Senator ALLARD. So it's not a protein, it's a carbohydrate?

Dr. WOODCOCK. Yes.

Senator ALLARD. Does Chondroitin have any protein in it?

Dr. WOODCOCK. Chondroitin is—I'll have Dr. Nasr discuss the chemistry.

Dr. NASR. Both Chondroitin Sulphate and Dermatan Sulphate and Heparin have similar complex carbohydrate structure.

Senator ALLARD. They don't——

Dr. NASR. No protein.

Senator ALLARD [continuing]. No proteins in Chondroitin. But it's a cartilage; that surprises me.

Dr. NASR. It's extracted from a——

Senator ALLARD. Is it the same Chondroitin that you see in cartilage?

Dr. NASR. Yes it is. Chondroitin is extracted.

Senator ALLARD. And that's not a protein in cartilage?

Dr. NASR. There is a protein in cartilage, but there is no protein in Chondroitin.

Senator ALLARD. In the——

Dr. NASR. The manufacturing process makes sure to eliminate the protein from the carbohydrates.

Senator ALLARD. Interesting. OK. But you have no qualms about the purity of protein on today's market. Do you see a risk at all, currently?

Dr. WOODCOCK. With Heparin?

Senator ALLARD. Yes, Heparin. Today, you would not hesitate to license Heparin and make it available by giving your approval; is that correct?

Dr. WOODCOCK. Heparin is an essential drug.

Senator ALLARD. Yes.

Dr. WOODCOCK. So we must have it available on the U.S. market. The testing that we've put in place, any contaminated lots of Heparin have been removed from the U.S. market and testing will assure that new contamination with Chondroitin Sulphate will not occur.

Senator ALLARD. OK. The Chinese government has disagreed with our scientific findings. Are there some legal reasons why they would deny our science, or is it pretty much a bona fide scientific disagreement or are there some trade reasons? Can you elaborate on why you think they would be so quick to deny the results of our scientific studies?

Dr. WOODCOCK. They had analytical results that led them to question the association between the contaminant and adverse events. They agree that there is a contaminant, in the Heparin, but they tested one batch that was associated with adverse events and they didn't find any contaminant in it.

Senator ALLARD. I see.

Dr. WOODCOCK. That led them to question the link. Now we have tested that lot in three laboratories, and they confirmed that it's contaminated. Basically, they're questioning it because they have different test results than we do, but we stand on our test results.

Senator ALLARD. I was just kind of curious if you felt that maybe there are some legal or trade reasons why they would be so persistent in denying that. Your response helped clarify that.

My time has expired.

Senator Brown [presiding]. Thank you, Senator Allard.

Senator Alexander.

Senator ALEXANDER. No questions.

Senator BROWN. One other question of the witnesses before we bring the next panel up. Is this explosion of imports of food and pharmaceutical ingredients, chemicals mostly, is this a function—is this all about cost to American companies? Or is this about an ability to get access to the chemical components that we need?

Dr. WOODCOCK. To a great extent it's about various cost factors, there are different environmental regulations in different parts of the world, there are other different requirements, the labor costs are lower, developing countries——

Senator BROWN. What do you mean by environmental rules in other parts of the world? You mean, we're more stringent here so we go abroad to get components for prescription drugs——

Dr. WOODCOCK. That's my——

Senator BROWN [continuing]. Somewhere else——

Dr. WOODCOCK [continuing]. Understanding.

Senator BROWN [continuing]. Because of weak environmental laws?

Dr. WOODCOCK. Well, you asked why companies are outsourcing and how it might be related to costs, and that one of the cost factors, we understand, is that very lower, less stringent standards exist in some parts of the world.

Senator BROWN. Think about what you just said. I mean, if it's about costs and it's about labor costs, I find that a bit objectionable when seven people in Toledo apparently have died from some of these contaminated ingredients, and I find that objectionable enough.

Do you believe or have you heard from American companies that they've gone abroad for chemical ingredients that end up in pharmaceuticals because of weaker environmental laws in those countries or weaker production outside of labor costs?

Dr. WOODCOCK. I have not heard from pharmaceutical companies, I have heard from analysts of that industry, who have a laundry list of why this wave of outsourcing has occurred. FDA has not really——

Senator BROWN. I caught your response, I understand.

Dr. WOODCOCK [continuing]. Economics, so we——

Senator BROWN. You know a lot about this.

Dr. WOODCOCK. That's what we've been told, yes.

Senator ENZI. Since you asked that question——

Senator BROWN. Senator Enzi, certainly.

Senator ENZI [continuing]. I need to emphasize some education a little bit here as well.

It's my understanding that some of the pharmaceutical firms are having trouble finding the kinds of engineers and scientists in this country. With our H1B and other visa problems, they can't get them into this country to do them, so the only option is to go somewhere else and do them, because if you don't have the technical people, you can't do it. I think there are more ingredients than just the environmental factors and, you know, we need to work on all the ingredients.

Senator BROWN. Sir, thank you for that. I don't believe for a minute it's all environmental factors, I think it's—I guess the question I mainly have, if it's cost more than availability, and Senator Enzi's point is well taken—if it's cost more than availability, that's one issue. When you cut in and slice into what the cost issues are, if it's labor costs, that's one thing.

If it's the cost to avoid various kinds of health and safety regulations, think of the irony there, American companies go abroad to make ingredients, and they can make them cheaper abroad because of environmental issues, and then they sell them back to us for our children, for our parents, for our families. I just think that's a pretty interesting question.

Other comments, Senator Allard.

Senator ALLARD. Mr. Chairman, I want to follow up just a little bit.

You mentioned that you have a hard time getting employees for the FDA to want to go to China.

Dr. WOODCOCK. Well, foreign inspections in general.

Senator ALLARD. Is language an issue? Does the Department of State help your employees learn Chinese in order to get over there? How do your employees become fluent in that language?

Dr. WOODCOCK. We can hire employees who are fluent in Chinese, and we have a very diverse workforce at the FDA, and we have employees who are fluent in most languages around the world.

I think much of our problem is developing an inspectorate who is willing to travel all the time. I mean, that's something that many people are not able to do, and go to these foreign countries and do these inspections. It's a difficult life to do that.

Senator ALLARD. OK, thank you.

Senator BROWN. I have one last question, would anyone be able to estimate how much—I imagine this might be USDR more than you, but how we can get to this—what the total amount of imports for pharmaceutical ingredients—chemicals, potentially contaminated pharmaceutical ingredients—would be coming from China to the United States? You would have no record of that or ability to know that, I assume.

Dr. WOODCOCK. Well, we hope that the kind of information technology system that we need to control this and to make sure we can regulate it properly—we need to know that kind of information. I can tell you, we don't know that right now.

Senator BROWN. Is that your responsibility to know it or should another Federal agency give that to you?

Dr. WOODCOCK. We need to know it from a technical point of view. We should not let any ingredient in the country, unless it's coming in here for a legitimate purpose, without knowing how it's going to be used.

We need to have a database that can verify that, so when pharmaceutical ingredients traverse our borders, we know we have control over that, we know what it's for, and it's legitimately in this country.

Senator BROWN. I would like to work with you on trying to figure that out. I think—when you think about this—if we knew a couple of facts here, what is the cost of the ingredients imported? I'm not talking about electronics or toys or anything like that—what are the costs of the ingredients imported? How much do American companies save by outsourcing these jobs—outsourcing this work, which they didn't do before? How many public dollars are spent to protect the public because of some companies decisions to outsource these jobs and outsource this—not these jobs—this work?

I think we'd learn a lot about what we really want to do, even to the point of, does it make sense that none of this be outsourced because of costs to taxpayers, deaths, illnesses, and ultimately, all of those factors, and where does that take us.

I would like to work with you on figuring those questions out.

Dr. WOODCOCK. Thank you.

Senator BROWN. Thank you, I appreciate this panel being here. Thank you very much.

Dr. WOODCOCK. Thank you.

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Senator BROWN. On the second panel, Glenn Morris is a Professor at the University of Florida, head of the Emerging Pathogens Institute, he was at the U.S. Department of Agriculture in the Clinton administration, helped found FoodNet at the CDC, and wrote the food portions of the recent FDA Science Board Report.

Bill Hubbard is a former FDA official with over 30 years experience at the agency and has testified in front of House and Senate Committees many times.

Bob Brackett, now of the Grocery Manufacturers Association, Dr. Bob Brackett has formerly led the Food Safety Center at the Food and Drug Administration.

And Gerry Migliaccio is Director of Quality at Pfizer.

Welcome all of you, and Mr. Hubbard, we will begin with you.

STATEMENT OF WILLIAM K. HUBBARD, FORMER ASSOCIATE COMMISSIONER FOR POLICY AND PLANNING, FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Mr. HUBBARD. Thank you, Senator Brown. I have a written statement, but I was asked to make very brief remarks, so I will keep them very brief.

We have this tremendous contradiction in which we have built this enormously effective safety net for foods and drugs in the United States called the FDA that works very well. Yet, we have not given them the means to regulate drugs and foods from abroad at a time in which 80 percent of our drugs are coming from abroad, either in finished pharmaceuticals or the raw materials. Increasingly, our foods are coming from these foreign sources.

As Dr. Woodcock said, we've built this domestic system, but then as all of these imports have become the principal source of some of these products, we have not then moved to build a similar system for imports. I think we're at great risk because we essentially have a largely unregulated supply, in some cases.

The Heparin example, I fear is a sad but good example of a case study of the peril that our citizens are in. It originated in a developing country, which does not have a long history of regulation in production of these products. There was no regulation in that country, they don't regulate this Heparin that was being sent to us. There were tremendous profits to be made by substituting cheaper ingredients, and FDA sees that all the time with foods and drugs, where substitutions of cheaper ingredients occurred. You'll all remember the Diethylene Glycol, which killed many children in Haiti, Panama, Nigeria, and other places.

There was no FDA inspection of this facility, and you have little likelihood that the counterfeiter is even going to get caught, and even less likelihood that the counterfeiter is going to be punished if he's identified.

I suggest to you that this is going to happen again, and perhaps again and again, because we simply don't have a system of infrastructures set up to strengthen the FDA. The risk of even greater numbers of illnesses than the 81 we saw here, I believe, are highly possible. Just imagine if these counterfeiters, instead of trying to make a buck, wanted to simply kill or injure Americans. I suggest to you, it wouldn't have been all that hard, and the impact could have been catastrophic.

I urge the Senate to consider some ways of strengthening the FDA and bring some sort of system in place over these products that largely does not exist today.

Thank you.

[The prepared statement of Mr. Hubbard follows:]

PREPARED STATEMENT OF WILLIAM K. HUBBARD

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 Alliance 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 Alliance 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 is comprised of three primary principles:

1. *Strictly regulated human testing and thorough FDA review, of drugs before they can be marketed.* FDA takes great care that new drugs meet the required standard of safety and effectiveness, and as such has been recognized as the "gold standard" for drug approval. Further, with the resources Congress provided for additional medical staff via the Prescription Drug User Fee Act, FDA now approves new drugs as fast or faster than anywhere in the world, meaning that Americans have first access to new medical breakthroughs while retaining the safety assurances that our citizens expect.

2. *Postmarket monitoring of drugs once they are marketed to assure that the approval decision was appropriate.* Congress has recognized that more information about a drug's safety will become available through the widespread use that occurs after its approval, and has instructed the agency to affirm that the approval decision was appropriate by tracking each drug's post-market safety profile. If safety concerns are identified that were not seen in the initial FDA review, the agency can remove a drug from the market, or otherwise intervene to ensure its continued safe use (such as through warnings or restricted distribution).

3. *Rigorous oversight of drug manufacturing, to assure that the drug approved by the FDA is the one that is actually manufactured and is of consistently high quality.* A drug must be manufactured under specific controls mandated by FDA—known as Good Manufacturing Practices (GMPs). 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. 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 as much as 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:

• Last year's 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 in 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] As the *New York Times* reported in 2007, the counterfeit glycerin was traced through a pipeline "from the Panamanian port of Colon, back through trading companies in Barcelona, Spain, and Beijing, to its beginning near the Yangtze Delta in a place local people call 'chemical country'."

• In just the past 2 years, seizures of fake drugs in the EU went from 500,000 tablets to almost 3 million. In addition, the UK's version of our FDA has recently been forced to conduct large scale recalls of counterfeit drugs that have made their way into their health care system.

• 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.

• Many of our citizens are lured to purchase prescription drugs directly, via the Internet, from suppliers around the world, often masked as Canadian or European pharmacies, but in reality providing counterfeit and substandard drugs from some of the darkest corners of the globe.

• Within China itself, deaths from counterfeit and substandard drugs have often been described; some reports place them as high as 200,000 to 300,000 annually.

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 nations' consumer goods. Here in the United States, it is estimated that 40 percent 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

[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.

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.

FDA AND IMPORTED DRUGS

At a time in which drug safety problems overseas have become more and more prevalent, the United States has seen a massive change in sourcing of its pharmaceuticals. Today, the vast majority of our drugs 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. 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?

Much of the recent concern about the quality of imported drugs focuses on whether FDA is capably regulating those products. I think not, but the reason for their failure is a critical piece in our understanding of how to correct the problems. We must recognize that FDA is asked to regulate these products with a law whose 70th anniversary is this year—a time in which there were few drugs being made anywhere in the world, and none being imported into the United States. The system created in 1938, with origins dating all the way to the turn of the last century, authorized FDA to examine imported drugs at the border and refuse entry to any drug that "appeared" to be unsatisfactory. Thus, the law placed the responsibility on the FDA to catch a problem and stop the drug's entry into our country, as opposed to asking the foreign manufacturer to demonstrate that they were taking care to follow established standards for drug production. So, while domestic drug manufacturers are held to a high standard of drug safety, with regular GMP inspections, foreign producers often need worry only about the remote possibility that an FDA inspector at a border crossing will find a problem and stop the drug's entry. Moreover, a domestic drug manufacturer using foreign ingredients can adhere to strict quality control procedures, yet be victimized by a contaminated ingredient that was unsuspected.[2]

More specifically, we have failed to provide FDA with the appropriations and other tools it needs to carry out the mission we have assigned to them, such as:

- Staff to conduct regular inspections in foreign facilities as are now done for domestic manufacturing plants. The Food, Drug and Cosmetic Act dictates that each U.S. drug manufacturer be inspected at least every 2 years, but the current rate of foreign inspections is infrequent at best. Thus, we are buying ever larger percentages of our drug ingredients from producers in developing countries who receive virtually *no* FDA inspection, despite a congressional determination that domestic manufacturers be inspected regularly.
- Modern IT systems that would allow FDA to effectively track and monitor the production and movement of imports. The import data system 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;
- Registration procedures for foreign drug manufacturing that would allow us to know who is making drugs for our market, where they are located, and what they are manufacturing; and
- Port inspectors to examine the almost 20 million annual shipments of foods, drugs, and other products that FDA is expected to regulate. For over 400 ports of entry, FDA has only 450 inspectors, meaning that most ports aren't staffed at all and many can be staffed only part time.

THE HEPARIN EXAMPLE

We are, of course, especially mindful today of the recent deaths from contaminated heparin. It is, sadly, a good example of the problem FDA faces in assuring the safety of imported drugs. Indeed, I believe one could use the well worn cliche of a "perfect storm" in describing the conditions upon which the heparin incident unfolded—initial extraction of heparin on pig farms that have been described as "primitive," no regulation by authorities in the producing country, no FDA inspection of the heparin exporter's manufacturing facility, and violative conditions found

[2] There is a long history of illegal additions and substitutions to our foods and drugs from foreign sources, ranging from illegal antibiotics in seafood, to the aforementioned antifreeze for glycerin, to the polysaccharide inulin in apple juice, to melamine in pet food, and most recently chondroitin to heparin.

by FDA in the manufacturing facility when subsequently inspected. When you add to that the technical capability of chemists to modify and substitute chondroitin for heparin, the resulting profit margin by using cheaper ingredients, the low risk of being caught substituting another ingredient, and the even more remote likelihood of being punished by U.S. authorities, one could accurately conclude that there was highly fertile ground upon which this could occur.

I cannot overemphasize the disparity between such conditions and those in the United States. While certainly FDA has at times found U.S. manufacturing facilities in violation of GMPs, the circumstances here are far different. U.S. drug manufacturers accept the need for high standards in drug development and manufacturing and generally adopt those standards faithfully. Indeed, drugs manufactured in the United States are subject to a long list of stringent regulatory requirements, and failure of any of those requirements will render the drug "adulterated" and thus illegal in this country. Moreover, 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

We must find a way forward to ensure that drugs made with foreign ingredients meet the same high standards as those of fully domestic origin, by assuring the enforcement of the rules that govern drug production and the promulgation of needed new rules. 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 some less developed countries 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 without a strong counterpart to the FDA 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—rigorous control of pharmaceuticals within a system closed to unregulated and unscrupulous suppliers and overseen by a strong FDA.

More precisely, I urge you to consider the following ideas:

1. **An immediate infusion of new appropriations for FDA's drug oversight activities.** As FDA's Science Board recently concluded, the agency is massively underfunded, and the paucity of resources for overseeing imported drugs is particularly glaring. Indeed, despite the fact that such a large proportion of our drug supply is of foreign origin, FDA's funding for regulating imported drugs is less than 2 percent of the agency's budget.

2. **A requirement for GMP inspections of foreign drug manufacturing facilities, with an immediate focus on drugs made in countries without a history of safe drug production and internal regulation.** Without such inspections, we essentially have no oversight of those manufacturers. A GMP inspection is far more than just a snapshot of that facility the day the inspector arrives. It is a detailed survey of how that plant has been operating for months, which allows a realistic conclusion about whether that facility can and does follow accepted drug production procedures. Relying on testing by the FDA or the U.S. drug company that receives the foreign ingredients is not a substitute for examining the source of production.

3. **Creation of a Foreign Inspectorate for the FDA that is dedicated to inspecting foreign manufacturing facilities.** Currently, FDA must utilize its domestic inspection force to travel overseas to conduct inspections. That practice is expensive and often a hardship on inspectors. The agency needs to recruit an inspection force that is hired and trained to do foreign inspections, and many will need to be housed in the countries with the greatest number of manufacturing facilities.

4. **A requirement that all foreign drug producers register annually with the FDA.** As the GAO has noted, FDA does not even have an accurate listing of drug manufacturers overseas. We need to know who is making our drugs, what compounds they are sending to our country, and where they are located.

5. **Appropriations and a specific congressional mandate to improve FDA's IT systems.** If we don't even have a system for capturing who's making these prod-

ucts, where they are, what's coming into our country, and related critical information needs, we can't hope to begin the process of improving our coverage of imports. 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 Science Board recommends increased appropriations of $800 million for FDA's overall IT needs, so there is a long way to go if FDA is to have state-of-the-art information systems, but we could at least start with funding an effective import information system.

6. **A vigorous mechanism for testing drugs for ingredients or contaminants that are not approved for that compound.** History has shown that processors, especially in less developed countries, can be adept at adding substances to increase the value of the product or decrease costs of production. But the danger of doing so is well established, and poses an enormous hole in the safety net we are trying to maintain.

7. **Clear authority for FDA to inspect in foreign countries.** This is a very simple proposition—if a nation sending pharmaceutical ingredients to our country is unwilling to allow FDA inspectors to examine facilities in their country for adherence to our safety standards, then those ingredients should not be allowed into the United States.

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. But history has shown that when FDA is given the resources and tools it needs to be effective, it will perform well and in doing so protect the health of those who depend every day on this critical agency.

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

STATEMENT OF J. GLENN MORRIS, JR., DIRECTOR, EMERGING PATHOGENS INSTITUTE, UNIVERSITY OF FLORIDA, GAINESVILLE, FL

Senator BROWN. I think your microphone's not on, Mr. Morris.

Dr. MORRIS. Sorry about that. As a physician, the Heparin issues are ones that are near and dear to my heart. I see patients and as a physician we've been concerned about this, but today I'd like to focus more on the food issues.

Again, we talk about food-borne disease outbreaks, but one of the things that concerns me is that while we saw an initial decline of overall incidents of food-borne diseases in this country after USDA HASSOP regulations over a decade ago, over the last several years these numbers have leveled off and we are essentially seeing the same numbers of food-borne disease cases as we have in the past.

We're in a situation where we're kind of at the status quo, and I think there's very much a need to think creatively about ways in which we can try to continue to see improvement in terms of the overall rate of food-borne disease in this country.

I think a key component of this is science. We need to have top quality science, both microbiologic and epidemiologic, much of that currently is not available.

The key elements in this that have already been brought out multiple times, are the lack of resources to be able to build an appropriate science base within FDA. The other component is to have the regulatory underpinnings so that FDA can do the job that it needs to do, in terms of protecting our food supply.

Again, FDA in terms of food, tends to be reactive. They respond to the crisis of the moment. I think what we need to be able to do is put in place a system that is preventive. I think FDA is headed in this direction, but at the moment has neither the resources nor

the statutory authority to be able to do what's necessary to reach that point.

[The prepared statement of Dr. Morris follows:]

PREPARED STATEMENT OF J. GLENN MORRIS, JR., M.D., MPH&TM [1]

Mr. Chairman, members of the committee, it is a pleasure to have the opportunity to provide you with information which may be of help in developing a common vision for the FDA role in food safety during the next decade. In particular, I would note the importance of the following issues:

• Food safety remains an important area of concern to the U.S. public. For the public, problems have been underscored by ongoing reports of foodborne disease outbreaks and major product recalls. However, from an epidemiologic perspective, it is perhaps more concerning that reported incidence rates for the major foodborne pathogens (based on 2007 FoodNet data) have remained relatively constant during the past several years, with some actual increases. This is in the context of initial declines in incidence rates in the early part of this decade, as compared with a 1996–1998 baseline. I was instrumental in the establishment of FoodNet in the mid-1990's, to serve as a means of assessing the public health impact of the new HACCP rules at USDA. While there are constraints on the interpretation of available CDC data, it is concerning that the initial declines in incidence rates seen in the years following the implementation of the USDA HACCP rule may have "leveled off," suggesting the urgent need for new and innovative approaches to protect the health of the American people.

• FDA, with responsibility for overseeing an estimated 80 percent of the Nation's food supply, must take the major leadership role in the development and implementation of such new approaches. As has been noted by multiple national committees (and by the FDA itself, in its Food Protection Plan), the FDA tends to be primarily reactive in issues of food safety: they spend most of their time putting out fires, rather than focusing on how to keep the fires from starting in the first place. There is a broad consensus that the agency must develop a pro-active, risk-based (and science-based) preventive approach to food safety. Initial steps in this direction have been taken by the agency, with the announcement of their Food Protection Plan. However, some key issues remain:

Development of a risk- and science-based approach to prevention requires science. More specifically, there is a need for high quality surveillance, both microbiologic and epidemiologic, to clearly identify and delineate problem areas. This, in turn, must be combined with a strong analytic capacity, both to guide the original data collection and to "make sense" of the data when it is collected. In this regard, many of the European countries (such as the Netherlands and Denmark) are well ahead of us, having in place well-designed surveillance systems that are used to regularly "tweak" the approaches and focus areas of the associated food safety regulatory agencies. Development of public health-based performance standards, which, long-term, are a critical element of a risk-based prevention system, requires an even higher level of sophistication in surveillance and analysis. Unfortunately, the capacity at FDA for such analysis is limited, and there is at best a clouded vision of what is needed for development of such systems.

As is true for many things in government, **development of risk-based systems will require money**—including substantial "up front" funding to get new systems in place. Long-term, there is little question that implementation of risk-based approaches will be cost-effective, both in terms of the agency budget and the reduction in costs associated with foodborne disease, but it will cost money to get there. I had the privilege of serving on the FDA Science Board Subcommittee on Science and Technology, which was responsible for the November 2007, report, "FDA Science and Mission at Risk." I strongly concur with the findings of the report. As the report has been widely circulated, I will not repeat the conclusions, other than to emphasis the critical need for adequate funding if the FDA is to continue to do its current job appropriately, let alone move forward with a vision for the future.

[1] Dr. Morris is Director of the newly established Emerging Pathogens Institute (EPI) at the University of Florida, Gainesville, where he is also a Professor of Medicine (Infectious Diseases). From 1994–96, Dr. Morris worked with the Food Safety Inspection Service, USDA, on development of the new HACCP regulations, and was instrumental in the establishment of FoodNet, the national surveillance system for foodborne illness. He has served on four National Academy of Sciences expert committees dealing with food safety, and currently serves on the Institute of Medicine's Food and Nutrition Board. Most recently, Dr. Morris served as a member of the FDA Science Board's Subcommittee on Science and Technology, which was responsible for the February 2008 report "FDA Science and Mission at Risk."

While there is unquestionably a need for science, and the funding to support that science, we, unfortunately, find ourselves in a situation where there are even more basic steps that must be taken to move the agency to a point where science can be applied. In this context, **I strongly applaud the efforts of this committee to provide the necessary legislative mandate for the agency to begin to move toward a preventive, risk-based future.** At a very simplistic level, there is a need for legislation that will require inspections at consistent intervals, and give FDA the tools necessary to recall products that may contain pathogenic microorganisms or toxin materials. Moving up from there, there is a need to bring companies into the creation of a vision for improved food safety, with a willingness to assume responsibility for identifying potential foodborne hazards within their products. Ultimately, a smoothly functioning risk-based system will include key components of HACCP, with strong industry buy-in and performance monitored by public health-based performance standards.

We have a long way to go to reach this point, both in terms of science and regulatory structure. However, there is a need to get started—to depart from the *status quo*, and to begin to apply innovation and creativity to an inadequate and antiquated system. I applaud this committee for beginning to move in this direction.

Senator BROWN. Thank you, Dr. Morris.

Dr. Brackett.

STATEMENT OF BOB BRACKETT, PH.D., SENIOR VICE PRESIDENT AND CHIEF SCIENTIFIC AND REGULATORY AFFAIRS OFFICER, GROCERY MANUFACTURERS ASSOCIATION, WASHINGTON, DC

Dr. BRACKETT. Thank you, Senator Brown.

I think it's safe to say that the food industry is committed to work with Congress in addressing some of the new challenges that have been already identified, especially with those rising imports, as you've mentioned, and also change in consumer preferences. We're also committed to food safety reform, but believe that risk-based approaches to the prevention, as has been mentioned earlier, of contamination should continue to be the foundation of our food safety strategies, rather than reaction.

In particular, we have several suggestions—including reforms that we think should be tackled, one of which is—first, we would urge you to give FDA the power to establish safety standards for fresh fruits and vegetables.

Second, that you require every food company have at least a written food safety plan that is available to FDA for their review.

And third, we would urge you to require every food importer to police their foreign suppliers and to document, for FDA review, their food safety controls. We believe that these, and some of the other recommendations that were included in our written testimony, would significantly reduce the risk of contamination, and more importantly, food-borne illness.

Clearly, FDA is going to need more resources if they're going to be able to accomplish this mission. Having said that, we are opposed to proposals to tax food companies, food facilities, and food imports, including the registration and import fees that have been proposed in the discussion draft of the Food and Drug Administration Globalization Act.

Even though we do actually share the goals of the discussion draft, we have a number of concerns, and I would really like to raise three at this point.

One is, while we support the requirements of a food safety plan, subject to FDA review, we oppose giving FDA inspectors the power to prescribe the specific safety controls that would be used.

Two, we oppose the proposals to impose a re-inspection fee and civil penalties that would increase the cost of food, but will not have any impact on the safety of the food.

And three, we're very troubled by proposals to effectively require that all foreign and domestic food facilities obtain third-party certification, regardless of risk. This would be a significant waste of resources that could, instead, be dedicated to more effective food safety measures.

The food industry is willing to accept new mandates to improve the safety of foods, including new mandatory safety standards for fresh fruits and vegetables, and to police our foreign suppliers. At this point, we are very grateful for the opportunity to testify and to work with you and with the staff, both on the discussion draft of the Food and Drug Administration Globalization Act, as well as discuss some of the alternatives that we think would improve the safety of our foods overall.

Thank you.

[The prepared statement of Dr. Brackett follows:]

PREPARED STATEMENT OF ROBERT BRACKETT

Thank you, Mr. Chairman. My name is Robert Brackett and I am Senior Vice President and Chief Science and Regulatory Affairs officer for the Grocery Manufacturers Association.

We commend and share your commitment to ensuring the safety of our Nation's food supplies and agree that a strong, adequately funded Food and Drug Administration (FDA) is fundamental to achieving this goal.

Food and beverage companies already implement a variety of food safety measures and controls to ensure the safety and quality of our products and ingredients. Ensuring the safety of our products is our most important priority. We agree that Congress must take steps to help FDA and the food industry address new challenges posed by rising food imports and changing consumer preferences. We believe that a risk-based approach to the prevention of contamination should continue to be the foundation of nation's food safety strategies.

We are grateful for your willingness to work with us to craft food safety legislation. While we support giving FDA additional resources, we strongly oppose placing annual taxes on food facilities or food importers to finance FDA operations. All Americans, not simply food companies, benefit from improvements to our Nation's food safety programs. We believe the costs of FDA inspections and research should be financed from general tax revenue, not from taxes imposed on food importers or facilities. While we support increased resources for FDA, we strongly oppose food taxes and "fees" that are not tailored to provide a government service to our industry and that will likely compound food costs at a time of record food inflation.

While we support additional regulation of food companies and importers, we oppose overly prescriptive new food safety requirements and oppose providing FDA inspectors with broad authority to review the adequacy of food safety plans. While we support the requirement that all food companies have a food safety plan, we believe food companies should be given the discretion to identify appropriate safety controls and measures beyond those controls and measures already required by regulation. Prescriptive, across-the-board new regulatory requirements will stifle innovation, divert resources from proven food safety measures, and will increase food costs at a time of record food inflation.

We are also very troubled by proposals to require FDA or third-party certification for all food facilities, regardless of risk. In particular, we are concerned that a proposal last week by Chairman Dingell to require all foreign and domestic food facilities to obtain certification from FDA-accredited certifying agents would exhaust FDA resources and would improperly delegate FDA responsibilities. Because importers who fail to seek certification would face severe import limitations and unworkable testing requirements, the "voluntary" program outlined in Chairman Dingell's Discussion Draft is effectively mandatory. Rather than using public resources to

strengthen our public food safety system, such proposals would effectively replace FDA with privately controlled and operated certifying agents with the power to determine whether a facility complies with Federal law.

A massive across-the-board certification requirement that ignores risk is unworkable and wasteful of public and private sector resources. While there is a role for third party audits in our food safety system, we believe this role should be linked to demonstrated need, such as the certification of imports of certain high risk foods. Effectively requiring all domestic and foreign facilities to obtain certification would demand the creation of an unprecedented private army of third-party certifiers that would be tantamount to creating a "shadow" government.

While we believe that some facilities deserve greater scrutiny than others, we generally oppose rigid inspection schedules and instead believe that FDA inspections should be based upon risk. We also strongly oppose needless civil penalties and reinspection fees. Food companies have powerful incentives to ensure the safety of food products and ingredients and current law already provides a wide range of enforcement tools, including seizure, injunction, and civil and criminal penalties. Giving FDA the power to assign massive fines and fees will dramatically alter the cooperative relationship between FDA and the food industry and will create a powerful incentive for FDA to find violations regardless of merit.

We also oppose broad new reporting and labeling requirements. In particular, we oppose proposals to dramatically expand scope of the new reportable food registry and oppose proposals to require food companies to identify the source of all ingredients. Food companies combine dozens of ingredients from more than 160 countries and change the source of these ingredients every day. Unworkable new labeling requirements will increase the cost of food without improving the safety of food.

We instead propose that Congress modernize our food safety system by making *risk* and the *prevention of contamination* the focus of our food safety strategies. In particular, we propose the following reforms:

• *One, we urge you to give FDA the power to establish safety standards for fruits and vegetables.* In particular, give FDA the power to establish food safety standards for particular fruits and vegetables—when risk and science demonstrate standards are needed. Under this proposal, FDA should be given the power to work with USDA and States to ensure standards are being met, and FDA should be given the power to work with States to tailor standards to meet local growing conditions.

• *Two, we urge you to require food company to have a food safety plan.* In particular, every food company selling food in the United States should conduct a food safety risk analysis that identifies potential sources of contamination, identifies appropriate food safety controls, verifies that those controls are effective, and documents those controls in a food safety plan subject to FDA review.

• *Three, require every food importer to police their foreign suppliers.* In particular, Congress should require that all food importers, subject to FDA guidance, document the food safety measures and controls being implemented by their foreign suppliers and should require food importers to make their foreign supplier food safety plan available to FDA. Food importers who demonstrate their products pose no meaningful risk should be eligible for expedited entry at the border so FDA can give greater scrutiny to high risk imports.

• *Four, build the capacity of foreign governments and enlist the help of the private sector.* In particular, Congress should direct FDA to develop a plan to help build the scientific and regulatory capacity of major exporters to the United States and should create a registry of private laboratories that meet FDA standards. In addition, FDA should enlist the help of accredited third party auditors to ensure that high risk imports meet Federal safety standards, to verify the contents of foreign supplier safety plans, and to help identify those imports eligible for expedited entry.

We also believe that Congress should give the Secretary new powers to address bad actors. Although food companies routinely recall contaminated products, we believe Congress should give the Secretary the non-delegable power to order a recall, subject to due process protections, when a product poses the risk of severe health consequences of death and the company has refused to conduct a recall.

Mr. Chairman, we are grateful for the opportunity to work with you to promote a risk-based approach to food safety regulation and to allow FDA the flexibility to respond to emerging risks in the manner that most efficiently uses the agency's precious resources. We look forward to working with you to develop and implement improvements that will make risk and prevention the focus of our Nation's food safety systems.

SUMMARY

Food companies support efforts to modernize our food safety system by making *risk* and the *prevention of contamination* the focus of our food safety strategies. In particular, we propose the following reforms:

• *Give FDA the power to establish safety standards for fruits and vegetables.* In particular, give FDA the power to establish food safety standards for particular fruits and vegetables.

• *Require food companies to have a food safety plan.* In particular, every food company selling food in the United States should conduct a food safety risk analysis that identifies potential sources of contamination, identifies appropriate food safety controls, verifies that those controls are effective, and documents those controls in a food safety plan subject to FDA review.

• *Require every food importer to police their foreign suppliers and build the capacity of foreign governments.* In particular, Congress should require that all food importers document the food safety measures and controls being implemented by their foreign suppliers.

• *Give the Secretary new powers to address bad actors.* Although food companies routinely recall contaminated products, we believe Congress should give the FDA the power to order a recall, subject to due process protections, when a product poses the risk of severe health consequences or death and the company has refused to conduct a recall.

Although we support giving FDA additional resources, we oppose taxes on food facilities and imports and we are troubled by proposals to require that all foreign and domestic food facilities obtain third-party certification. We also oppose prescriptive new regulatory requirements, broad new labeling requirements, and civil penalty proposals that will increase food costs but will not improve food safety.

Senator BROWN. Thank you, Dr. Brackett.

Mr. Migliaccio, good to see you, thanks for being here.

STATEMENT OF GERALD MIGLIACCIO, VICE PRESIDENT OF QUALITY, EHS AND AGILITY, PFIZER, INC., PEAPACK, NJ

Mr. MIGLIACCIO. Thank you. I'd like to thank Chairman Kennedy and Ranking Member Enzi for inviting me to participate in this hearing. My name is Gerry Migliaccio, I'm the head of quality for Pfizer, Inc., the world's largest research-based biomedical and pharmaceutical company.

This morning I'd like to just summarize my written testimony, which describes our approach to ensuring a secure pharmaceutical supply chain.

Pfizer's reputation depends heavily on the quality and safety of the products it sells. We currently outsource about 17 percent of the manufacture of active ingredients in drug products. Whether we produce internally or outsource, a secure supply chain is paramount in protecting the patients who use our products.

The responsibility for assuring the security of the pharmaceutical supply chain is shared by industry and by FDA. As manufacturers in emerging countries enter and expand the global supply chain, both industry and FDA face significant challenges.

Companies in emerging markets are generally operating in developing regulatory environments with novice inspectorates. Many have rudimentary quality systems or none at all. Before a U.S. pharmaceutical firm can consider sourcing from these suppliers, it is imperative that the firm work with the suppliers to upgrade their quality systems and standards.

To accomplish this, Pfizer has taken steps to educate, to evaluate—and for lack of a better word—to enforce appropriate quality standards. We educated public workshops and private meetings with potential suppliers. We established clear expectations for

quality systems, including the requirement for them to manage suppliers of raw materials.

The evaluation of an active ingredient or drug product supplier is an essential element of Pfizer's quality system. The evaluation consists of a number of clearly defined steps.

Quality can not be tested into a product, it must be designed in and assured by effective quality systems. It is neither technically nor physically feasible to test for all potential adulterants in every active ingredient and drug product entering the United States, therefore, the integrity of the supply chain must depend on careful selection of contract manufacturers and suppliers, and reliance on the quality systems they have in place. Those quality systems must include direct management and oversight of raw material suppliers.

The Pfizer evaluation process is led by a dedicated quality unit and consists of a preliminary self-assessment by the contract manufacturer themselves, followed by a due diligence audit, action plans, and follow up audits, and finally, product quality assessment.

If approved, routine oversight is provided by the quality unit and may include on-site visits during the manufacture of Pfizer products.

Contract manufacturers and suppliers are eager to enter the global supply chain. Pfizer grants access only to those who have demonstrated that they have achieved the standards required, and that means both quality and environment health and safety standards. The rigor provides significant economic motivation for would-be contractors to upgrade and maintain their facilities and quality systems and secure their supply chains.

We, at Pfizer, are admittedly moving in a very cautious manner when evaluating potential sources from developing countries, but it is imperative that we enforce our corporate standards in all countries.

Thank you.

[The prepared statement of Mr. Migliaccio follows:]

PREPARED STATEMENT OF GERRY MIGLIACCIO

I would like to thank Chairman Kennedy and Ranking Member Enzi for inviting me to provide this written testimony and to participate in today's hearing, "Restoring FDA's Ability to Keep America's Families Safe." My name is Gerry Migliaccio; I am the head of Quality for Pfizer Inc, the world's largest research-based biomedical and pharmaceutical company. In this testimony, I would like to outline Pfizer's approach to ensuring a secure pharmaceutical supply chain.

Pfizer currently operates 57 manufacturing sites around the world. To complement our internal manufacturing, we currently outsource the manufacture of approximately 17 percent of our active ingredients and drug products. The drivers for outsourcing include: sourcing flexibility, competitiveness, need for special technology, cost control and site divestitures. Pfizer's reputation depends heavily on the quality and safety of the products it sells. Whether we produce internally or outsource, a secure supply chain is paramount in protecting the patients who use our products. Industry and FDA share the responsibility for assuring the security of the pharmaceutical supply chain. As companies in emerging countries enter and expand the global pharmaceutical supply chain, industry and FDA face significant challenges.

Traditionally, pharmaceutical companies in the United States have sourced active ingredients and drug products from within the United States, from Europe, Japan and other developed countries. Our suppliers and contractors in these countries operate within sophisticated regulatory environments with highly competent

inspectorates. Most operate to internationally recognized standards established by the International Council on Harmonization (ICH). Therefore, they generally have effective quality systems that provide a high degree of confidence in the overall supply chain.

Companies in emerging markets are operating in a developing regulatory environment with a novice inspectorate. Many have rudimentary quality systems or none at all. Before a U.S. pharmaceutical firm can consider sourcing from these suppliers, it is imperative that the firm works with the suppliers to upgrade their quality systems and standards. To accomplish this, Pfizer and other companies have taken steps to Educate, Evaluate and for lack of a better word, Enforce appropriate quality standards.

EDUCATE

Industry and FDA share the responsibility to educate manufacturers and regulatory authorities in emerging countries. FDA's proposal to place resources in select foreign countries will certainly aid their ability to educate and train foreign regulatory authorities and manufacturing firms. Industry, working through public workshops and private meetings with potential suppliers, should establish clear expectations. Compliance with ICH quality guidelines, effective quality systems including management and oversight of the suppliers supply chain, and compliance with appropriate environment, health and safety standards are just some of these expectations.

EVALUATE

The evaluation of an active ingredient or drug product supplier, whether in a developed or developing country, is an essential element of a pharmaceutical firm's quality system. For Pfizer, the evaluation consists of a number of clearly defined steps that are articulated in a written standard operating procedure. The most important point to make regarding Evaluation is that you cannot test quality into a product; quality must be designed in and assured by effective quality systems. No amount of inspection and testing by itself will assure quality. It is neither technically nor physically feasible to test for all potential adulterants in every active ingredient and drug product entering the United States. Therefore, although we do a fair amount of statistically based sampling and testing, the integrity of the supply chain must depend on the careful selection of a contract manufacturer or supplier, and reliance on the quality systems they have in place. The quality systems must include direct management and oversight of raw material suppliers (the actual manufacturers, not commercial brokers).

Pfizer has a dedicated quality assurance unit to evaluate and provide oversight to contract manufacturers. That unit, which is divided into three groups located in the United States, Europe and Asia, provides quality professionals who speak the local language and understand local customs and closely follow the operating practices of our suppliers.

Pfizer initiates the process by providing the potential contract manufacturer a list of expectations and a self-assessment questionnaire. The response is reviewed and a decision made as to whether to proceed to the next step, a due diligence audit conducted by representatives from quality, manufacturing and other disciplines. This audit will examine the company's quality system including their sources of materials and control of their supply chain. (Frequently, Pfizer will insist that the contractor obtain materials only from Pfizer-approved sources.) At the end of the audit, the results are reviewed and a decision is made whether to continue with the evaluation. The decision to continue is based on a conclusion that either the firm is in compliance with Pfizer standards or the firm has committed to an action plan to close compliance gaps. If the latter, follow-up audits are conducted until a determination is made that the firm is in compliance. Only when compliance with Pfizer standards is established, will the evaluation of active ingredient and drug product begin. The evaluation includes testing of quality attributes as well as a review of the overall process validation. The evaluation process utilizes risk assessment models to assist in the approval or rejection of a potential contract manufacturer. Once approved, quality oversight includes ongoing evaluation of changes, deviations, and trends, as well as on-site reviews during production to ensure that standards are sustained.

ENFORCE

Contract manufacturers and suppliers are eager to enter the global supply chain. U.S. pharmaceutical firms should grant access only to those who have demonstrated that they have achieved the standards required. This rigor will provide significant

economic motivation for would-be contractors to upgrade and maintain their facilities and quality system and secure their supply chains. Pfizer admittedly is moving in a very cautious manner when evaluating potential sources from developing counties, but it is imperative that we enforce our corporate standards for suppliers in all countries.

Securing our supply chain through education, evaluation and enforcement requires a significant commitment of resources; this represents a necessary investment to fulfill our corporate responsibility to patients.

Senator BROWN. Thank you very much, Mr. Migliaccio.

The New England Journal of Medicine recently published, I believe it came out in the last few days, "Contaminated Heparin Associated With Adverse Clinical Events, An Activation of the Contact System." Let me just read one paragraph, which I think echoes Mr. Hubbard's words pretty well.

> "Urgent problems included an immediate and unknown risk to patients lives, a threat to the supply of a widely used essential drug, and the need for international cooperation of managing the integrity of a global supply chain. This crisis necessitates an urgent need to both understand the basis for these clinical events, and to prevent future occurrences."

Mr. Migliaccio, you said 17 percent of your active ingredients are outsourced?

Mr. MIGLIACCIO. Seventeen percent of our manufacturing—both active and drug product is outsourced.

Senator BROWN. OK. How much does Pfizer save a year by doing that?

Mr. MIGLIACCIO. Senator, first of all, it's not always driven by cost savings. In a number of cases, it's technology. We have to outsource certain operations that we do not have the technical capability to do. Certainly competitiveness and cost is a driver.

I do not have a number to present to you, I can research and get back to you——

Senator BROWN. I'd like that.

Mr. MIGLIACCIO. I don't have a number as to what outsourcing is saving us this year.

Senator BROWN. OK, I would like that.

You say that, technically, we were not able to do that.

When you made a decision, when Pfizer made a decision to begin buying ingredients from China, for example, was China technologically able to do that, at the time? And we weren't? Or did you go work with Chinese subcontractors to build that technological capacity, instead of building it here?

Mr. MIGLIACCIO. In the case of the most recent project we've been working on, the firm had a technical capability in steroid manufacturing.

Senator BROWN. "The firm," meaning the Chinese?

Mr. MIGLIACCIO. The Chinese subcontractor, had a technical capability in that area, so that's why we sought to outsource.

Senator BROWN. We did not?

Mr. MIGLIACCIO. We had that technical capability, but they would increase our competitiveness in the market.

Senator BROWN. So, that was about cost?

Mr. MIGLIACCIO. Yes.

Senator BROWN. Could you present to the committee, in writing, any examples of when you made a decision to go offshore—espe-

cially China, but not confined to China—but country, let's say, confine it to countries that don't have the food safety net that we do in this country. Take out countries with comparable FDAs, if you will, that went offshore—you made a decision to go offshore, because at that time the country where you were located, had technological capacity that we didn't as a country. I would like to see any list of those manufacturing of ingredients that you could come up with that way.

Mr. MIGLIACCIO. That's fine. It's generally not countries, but firms.

[The information requested follows:]

Following are examples of technology that Pfizer outsources due to either limited or no internal capacity.

- Devices (e.g. pre-filled syringes, inhalation devices)
- Lyophillization (freeze drying)
- Specialized packaging
- Soft gelatin capsules
- Specialized active pharmaceutical ingredient technology (e.g. biotechnology)

The majority of this outsourcing takes place in the United States and Europe.

Senator BROWN. Firms, but located in countries without the safety regimen of the FDA.

Let me get to one more point, and then I want to ask Mr. Hubbard a question. I think if you'll look at what's happening—there's a Professor at Ashland University, not far from where I grew up, in North Central, OH, who took his students—this chemist who teaches college chemistry, not graduate school, this was not graduate school, it was a college chemistry class—took them to stores at Halloween last year, at Christmas, and then at Easter, and bought toys in these stores, very inexpensive toys, and then the students brought the toys back and they tested them for lead. The tests were off the charts on a number—or at least 10 percent of these items, each time he did it.

I started thinking through this whole process. What's happened is Hasbro and other companies will outsource—American companies will outsource to China—to a country that doesn't have strong environmental worker safety laws—we know all of that. Then they will go to these Chinese sub-contractors, and they'll keep pushing these Chinese sub-contractors to cut costs. That's how we ended up with lead-based paint, in many cases, because it's cheaper to apply, cheaper to buy—all of that, cutting costs.

Then bring it back here with a weaker inspection system. Is that a fair characterization of the way Pfizer operates, too?

Mr. MIGLIACCIO. No sir, it's not. In fact, probably, to my—well, let me describe it in these terms. We may get an original business proposal from a firm anywhere around the world, including the United States. Once I insert my organization, the cost always goes up.

We have standards. And we insist that we achieve those standards. When we go into, whether it's China or Ireland or the U.K., we are evaluating, and it's all about presence. Dr. Woodcock said it all earlier as well, it's all about having a presence in those countries.

We have an organization that is—I have 66 quality professionals that are spread around the world managing our contract manufac-

turers. They are on-site, they are there, and we're enforcing our quality standards, we are enforcing environmental health and safety standards that exceed, well exceed, local requirements. In fact, it adds to the cost, in some cases significantly, but it's the standards that we've established.

Senator BROWN. Thank you Mr. Migliaccio.

Real quick, Mr. Hubbard, I'm hearing—I do a series of round tables around Ohio—I invite 15, 20 people in communities all over the State and just ask some questions for an hour and a half, and I've begun to hear people bring up this whole dental implant issue with lead. I heard it last week and earlier this week in Perry County, in a little town southeast of Columbus. What's the best solution for dealing—is it—one, it is an increasingly extensive problem, and two, what's the best way to deal with it?

Mr. HUBBARD. Well, various dental amalgams have been suspected of having problems, they had mercury in them and I believe the dental industry's been removing the mercury. I'm not familiar with this particular lead issue. I think you said that you thought the bridge material may have come from overseas?

Senator BROWN. That's what my understanding is. I don't know enough yet to know, for sure.

Mr. HUBBARD. The FDA clearly has limits for lead contamination in all of its products, foods and drugs and medical devices, so it may well be that that was a violated product that was missed.

Senator BROWN. OK.

Senator Enzi.

Senator Enzi [presiding]. Thank you.

First of all, I'd like to thank Dr. Woodcock for staying to hear the second panel. It's an unusual treat for us to see the person that has some capability in this area listening to what the others have to say. Listening isn't a talent that happens a lot around here, so thank you very much.

Let's see, I'll start off with a question for Dr. Brackett. I agree with your suggestion that these food safety activities should be focused on high-risk foods or facilities. Could you tell me more about how you classify a food or facility as high-risk?

Dr. BRACKETT. Sure, Senator Enzi. There's a number of different factors that can be added into that, one of which is the characteristics of the food itself, that is, if it supports the growth of microorganisms or if it's been associated with food-borne illness in the past, that automatically would raise it up.

Also, the history of the company itself and what their compliance record has been in the past might also raise that up to a higher class of risk. Then there are those types where there's been a history, where there's been little or no problem of food-borne illness, where the compliance history has been good, they should not be getting the same sort of scrutiny that one that is at that higher risk should be getting.

Senator ENZI. I always appreciate that clarification, that there are different levels and some people deserve inspections more than others.

Mr. Migliaccio, I don't have any "are you still beating your wife"-type questions for you.

[Laughter.]

I've been trying to picture, I know that part of the process with Heparin was to have people cut up pig guts and strip them all day. I'm trying to figure out if there's anybody in Wyoming that's interested in that kind of a job, or anybody in Ohio that's interested in that kind of a job.

You describe the strides that Pfizer takes to ensure the quality, safety, and integrity of the products you manufacture, which extends to qualifying the suppliers that you use. In your view, are the activities and steps you describe typical of the pharmaceutical manufacturers, including manufacturers of generic products and active pharmaceutical ingredients?

Mr. MIGLIACCIO. Senator, I can only speak with respect to companies that I'm closely associated with, and those are generally PhRMA member companies. Generally, in discussions that I have with my counterparts in PhRMA member companies, they all have comparable quality systems in place.

Senator ENZI. Is part of the incentive that's built into this thing the hopeful good faith that people are going to have in your company to continue to buy your products?

Mr. MIGLIACCIO. It's our reputation, Senator. I mean, if we have recalls or deaths because of contaminated product, it is our reputation, and it's our patients. We want all of our patients to feel secure that when they see the Pfizer logo on a product, they know it's the highest quality.

Senator ENZI. Again, I'll be providing all of you with some questions that I'm not going to have time to ask, and some of them are more technical than what people would even be interested in knowing around here. I know there have been instances in the past with, maybe not with your pharmaceutical company, but others, where some of that integrity has been lost. I'd like to have some of the cost figures that are involved in that, just to show what kind of incentive there is to do this qualifying of suppliers and these activities that you've mentioned, but I'll ask that one in writing.

I'll go back to Dr. Brackett. In your testimony, you indicate support for requiring every company to have a food safety plan, and you indicate that the plan would be subject to FDA review. However, you also State that you oppose providing the FDA inspectors with broad authority to review the adequacy of the plan. What am I missing?

Dr. BRACKETT. Well, I guess maybe you misunderstood what I said, or I wasn't very clear. We actually do think that there should be a food safety plan with each part of the industry, each company.

We don't oppose them having the review, I think that's the purpose for having the plan. What we oppose is having the agency have the ability to dictate what the response would be or what the specific remedy would be, technologically. We think that within the food industry there is the expertise to solve the problem without the agency being very prescriptive. We often find that when a regulatory agency is very prescriptive, that sort of stymies creativity and new ways of achieving the same goal.

Senator ENZI. You're suggesting some flexibility with principles then, am I getting that right?

Dr. BRACKETT. Well, that's right. I think—the plan itself is like a plan for building a house, you can't build a house unless you

know where you're going, what you're going to do to solve the problem ahead of time. The food safety plan allows the company to look carefully at what the food safety problems might be, do a risk assessment, provide some way of preventing those problems from occurring, and then also knowing that the agency would have the chance to look over their shoulder and make sure that they're not trying to avoid addressing some of the problems, without providing a solution.

Senator ENZI. Thank you. As we've heard in the previous testimony, there are circumstances that changes would happen because some of the tests that would have picked up—or the chemicals had been doctored in such a way, perhaps, that they didn't—they were able to pass the tests and new tests were required in order to catch them.

Dr. BRACKETT. Yes, Senator, you make an excellent question, that as science moves forward, I think it's important for the industry to have the flexibility to adopt that new science, rather than being kept in the past by old dictates.

Senator ENZI. Thank you.

Mr. Migliaccio, I imagine your company's had quite a few laws and regulations to comply with, but as an industry leader, I would expect that you go beyond those requirements to institute best practices that meet very high standards. Could you describe the safety and quality measures that might go beyond FDA mandates?

Mr. MIGLIACCIO. Well, if you look at the GNP regulations, and if you look at the FDA's quality system guidance, they clearly call for the Quality Unit to oversee operations that are being done under contract, but they're not explicit. I think the fact that we have established an organization around the world who have a significant presence at our contractors, probably exceeds what most would interpret the regulations and the guidance to require.

Senator ENZI. I know that was kind of an unfair question. Again, I'll have some more detail I'll want to get out in that particular area.

I do have questions for the other two, too, but my time has also expired and other meetings call. I'm the last one here, so I will submit questions in writing, as will other members of the Senate, and we'll ask you to respond as promptly as possible so that we can look for solutions, so that we can do more hearings, so that we can get down to the principles that need to be taken on, and hopefully have some bipartisan support in making sure that our food and drug supply is as safe as possible.

I thank you all, and the meeting is adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF ROGER BATE, RESIDENT FELLOW, AMERICAN ENTERPRISE INSTITUTE AND RICHARD TREN, DIRECTOR, AFRICA FIGHTING MALARIA

Thank you Chairman Kennedy, Senator Enzi, and members of the committee for the opportunity of submitting testimony for this important hearing. Keeping American families safe, improving medical care and health outcomes is immensely important. Our testimony highlights the growing dangers of counterfeit and substandard medicines in the United States and around the world. We believe that in restoring the FDA's ability to keep American families safe, the U.S. Congress will not only save lives at home, but will help to improve standards of medical care and drug quality for many millions of people around the world, particularly the poor and vulnerable in Africa.

INTRODUCTION

The tragic deaths of 81 patients from tainted heparin treatment highlight the potential danger of cheaply produced, often counterfeit, medicine imported from abroad. Congress is indeed paying attention, as this hearing follows closely on Chairman Dingell's House hearing on April 22; yet we fear it may miss the point.

Importing finished medicines and the active pharmaceutical ingredients (API) used to make them, reduces price. And India and China have some of the cheapest production around. All three presidential candidates—Senators Clinton, Obama, and McCain—support making drug importation easier.

What they, and others, seldom acknowledge however, is the risk inherent in such importation, especially when done by individuals outside the secure supply chain. According to FDA, over half the drugs Americans buy over the Internet don't work; at least one North American death has been officially linked to drugs purchased in this way.

This episode exposes the ugly little secret that in the quest to produce cheap drugs, quality is sometimes sacrificed. Substandard and counterfeit drugs are prolific in many countries in Africa, Asia, and elsewhere, where government regulatory agencies are not as adept as the FDA, and businesses are not as vigilant as U.S. companies (such as Baxter, Covidien and B. Braun), all of which took the initiative by issuing precautionary recalls of heparin. In some European countries, notably Finland, incidence of counterfeit products may be as high as 8 percent of total pharmaceutical sales, although in the United Kingdom, like the United States, it is under 1 percent.

Companies are better positioned to source and import drugs than are patients, since they have experience, expertise—and reputations to maintain. Western governments and agencies, such as the World Customs Organization and Interpol, should continue to encourage vigilance in exporting countries; the FDA should send more inspectors to randomly check on drug production in China and India.

In the United States, high commercial and regulatory standards have limited counterfeits in the market. But this has led to complacency, and political opinion is now leaning towards allowing more third-party intermediaries to import drugs from overseas. This may reduce costs in the short run, but may also introduce more counterfeits. While regulators can oversee legitimate companies, they have very little defense against the myriad actors that importation encourages, including criminal operators. An unchecked drive for the cheapest drugs will increase the risk of more heparin-type incidents.

U.S. companies already import 40 percent of API from India and China, and this is expected to rise to 80 percent within a decade. While a few companies in both countries have the technical capacity to make good drugs and API, regulatory structures are weak, and their markets are plagued by counterfeit and substandard medicines which annually kill tens, maybe hundreds, of thousands of their residents.

American consumers benefit when U.S. companies import API from Asia, assuming these companies pass cost savings on to consumers. This system should continue. But there is a risk, and to deny it, or leave individuals to make the decisions, is folly.

DEFINING THE PROBLEM

What constitutes a "counterfeit" drug varies from country to country. WHO broadly defines a fake or counterfeit drug as "a medicine which is deliberately and fraudulently mislabeled with respect to identity and source. Counterfeiting can apply to both branded and generic products, and may include products with the correct in-

gredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging." For the most part, "originator pharmaceuticals," also known as branded pharmaceuticals, are the main target of counterfeiters, since they promise high profit margins.

As with any illegal activity, the scope of the problem is impossible to define with precision. Unofficial estimates from researchers on the proportion of counterfeit drugs in the pharmaceutical markets across the world range from a high of 50 percent to a low of 1 percent, with other estimates from reputable researchers at 40, 30, and 17 percent. WHO reported in 2006 that the fake drug industry has annual revenues of over $40 billion—a figure sure to increase as more cases of counterfeit drugs are investigated and reported. The U.S. Food and Drug Administration (FDA) reports that the number of open investigations into domestic counterfeit drugs jumped from about 5 per year in the 1990s to more than 20 by 2000; in 2004 alone, there were 58 documented investigations. WHO cites the Center for Medicine in the Public Interest's prediction that counterfeit drug sales will reach $75 billion globally in 2010—an increase of more than 90 percent from 2005.

THIS ROLEX MIGHT KILL YOU

Counterfeit drugs are commonly made and distributed by criminal gangs, who are attracted by the high profit margins of the trade. Many counterfeiters use fake Western addresses to impress patients and doctors in poor countries. These gangs also peddle other illicit items, such as narcotics, arms, and fake jewelry. Like fake Rolexes, fake drugs are often hard to identify. A fake Rolex will probably tell time, but when examined closely, most people can tell it is a fake. The ineffectiveness of fake drugs may be revealed only when a life has been put at risk. Fake drugs also undermine confidence in branded products and even entire health-care systems.

Counterfeit drugs contain little or none of the active ingredients of legitimate drugs, with varying consequences depending on the disease. An outright lack of active ingredients may cause death, particularly in infants. In some cases, the material substituted for the authentic active ingredient may be toxic, leading to allergic reactions or death. In July 2007, a 57-year-old Canadian woman died after ingesting counterfeit antidepressants and acetaminophen that contained toxic levels of aluminum, phosphorus, titanium, tin, strontium, arsenic, and other heavy metals. In the heparin case, the component substituted for heparin was not approved for medical use because it causes severe allergic reactions.

Too little active ingredient poses another problem. Low-strength medicines will only knock out the weaker strains of the parasite or disease, leaving the stronger ones to thrive and develop resistance to the drug. This means that even the genuine drug will be rendered useless to the patient; his or her only option will be to try to get access to vastly more expensive second-line drugs. If the disease develops population-level resistance, a whole drug class will be lost.

Dora Akunyili, the director general of the Nigerian National Agency for Food and Drug Administration and Control, astutely analyzes the situation in her country and elsewhere:

"The evil of fake drugs is worse than the combined scourge of malaria and HIV/AIDS put together. . . . Whereas HIV/AIDS can be avoided, and malaria can be prevented, fake drugs kill en masse, and anyone can be a victim."

Yet counterfeiting pharmaceuticals usually carries far lower penalties than producing and selling narcotics—and because it is just as lucrative, it is becoming a booming business. The extent of the problem is shocking: counterfeit drugs manufactured by South American narcotics gangs or unregistered chemical works in China have infiltrated legitimate supply chains and ended up in pharmacies, clinics, and hospitals all over the world. Even well-respected, high-quality pharmacies such as CVS and Rite Aid have been fooled in the past; the recent infiltration of fake heparin was effected through established, here-before reliable supply channels.

At present count, 81 deaths have been associated with violent allergic reactions to a heparin-like substitute introduced into active pharmaceutical ingredients manufactured in China and imported into the United States and other western countries, where it was used to manufacture medicines. The adulterated product passed standard quality tests and only after suspicious symptoms and deaths had occurred was the product tested further. FDA scientists determined that suspicious lots of API used to make the drug were imported from China and appeared to contain 5 to 20 percent of a heparin-like compound which mimicked heparin activity so closely that it was not recognized by routine testing.

Raw heparin is normally sourced from the intestines of pigs, while the contaminant—oversulfated-chondroitin sulfate—comes from the cartilage of the animal. It is more abundant and cheaper than raw heparin, and not registered for medical use

because it causes severe allergic reactions. The FDA was careful to avoid the word "counterfeiting," when pressed by reporters, but Dr. Janet Woodcock, its Director of the Center for Drug Evaluation and Research, noted that the Agency was "99 percent sure [the contaminant] is not a natural component that got in there as part of the purification process."

FDA inspection of the Changzhou, China facility of Scientific Protein Laboratories LLC (SPL), the company responsible for producing the suspect API, revealed insufficient standard-setting and a lack of good recordkeeping. On Monday, when the Chinese Government suggested that the problem may have originated within the United States, the FDA quickly responded by issuing a warning to SPL (and indirectly criticizing the Chinese Government) citing "significant deviations" from good manufacturing processes at its Changzhou facility and recommending disapproval of applications to manufacture other active pharmaceutical ingredients.

The FDA and affected companies appear to be managing the incident well, minimizing American exposure to suspect lots while ensuring that patients are guaranteed supplies of genuine drugs. On January 17, Baxter International voluntarily recalled nine lots of its injection multi-dose vials of the drug, and in late February, expanded the recall to all remaining lots and doses of the multi-dose product. Meanwhile, FDA investigated both the Wisconsin and Changzhou, China facilities of SPL; shortly thereafter, SPL's Wisconsin facility announced it was recalling the heparin it had distributed to a number of companies. The FDA also investigated a New Jersey facility to find out whether the heparin could have been contaminated by its packaging. The diligence appears to be paying off: no new deaths associated with the suspicious allergic reaction since the end of February have been reported (although the FDA has revised the total number of deaths attributed to the allergic reaction several times since then, probably earlier deaths now attributed to the contaminated product).

TRACKING COUNTERFEIT MEDICINES AROUND THE GLOBE

The problem of counterfeiting drugs is rampant in both developed and developing countries. In wealthier developed countries, counterfeiting most frequently affects "lifestyle drugs" such as hormones, steroids, erectile dysfunction, and anti-allergy medicines. In the 1990s, several deaths associated with the use of a fake version of the antibiotic gentamicin occurred in the United States. More recently, in May 2003, nearly 20 million doses of fake Lipitor, a cholesterol-lowering medication, had to be pulled from U.S. pharmacies. Altogether, because wealthy countries have stricter regulatory mechanisms, and since most patients in wealthy countries can afford branded medicines, counterfeits account for less than 1 percent of the market value—although 50 percent of Internet sales are estimated to be counterfeit.

In developing countries, the scale of the problem is disproportionately worse. The latest joint estimates by WHO, the Organisation for Economic Co-operation and Development, and the Pharmaceutical Security Institute show that more than 30 percent of medicines in some areas of Latin America, Southeast Asia, and sub-Saharan Africa are counterfeit. For Africa, data is scarcer, but the situation is similarly bad. In 2005, a random survey by Kenya's National Quality Control Laboratories and the Pharmacy and Poisons Board found that almost 30 percent of the drugs in Kenya were counterfeit. Some of the drugs were no more than chalk or water.

In poor countries, essential and life-saving drugs used to treat infectious diseases such as tuberculosis and malaria are often the drugs threatened by counterfeiting. Since the burden of these diseases is greatest in these countries, and because people tend to be disproportionately poor, they will often buy counterfeit drugs on the black market, despite poor quality and even appearance. In our anecdotal experience—poor family members of the very sick often buy anything they can afford rather than do nothing.

MALARIA: A CRITICAL EXAMPLE

A field survey from 2002 to 2003 showed that 53 percent of artemisinin-based antimalarials—the most effective treatment available—bought in several Southeast Asian countries were counterfeit and contained incorrect levels of the active ingredient. The authors noted that the problem seemed to have increased significantly compared with their previous survey in 1999–2000.

In 2006, researchers conducted a quality-control study of antimalarial tablet samples purchased on the black market in Angola, Burundi, and the Democratic Republic of the Congo. The results identify a variety of problems: dubious packaging, low content of the active ingredient, and substandard technological properties (including very low dissolution profiles). In a 2003 survey, researchers found that the active ingredient content in at least one of three formulations of counterfeit drugs tested

in seven African countries was below the minimum level recommended for the product.

Malaria claims over 1 million lives every year, mostly among children in Africa. The disease is entirely curable, but urgent treatment is necessary because the disease can progress very quickly, particularly in young children or pregnant women. In most of Africa, people procure their malaria treatment from the private sector, frequently paying out-of-pocket for poor quality medicines and sometimes for fakes. While most African countries have officially changed their malaria drug treatment policies to the new, effective artemisinin-based combination therapies (ACTs), most have not removed the less effective artemisinin monotherapies from their drug registries. Untested, unregulated and potentially dangerous medicines are frequently sold and are widely used. The problem of substandard treatment of malaria is of particular concern due to the dangers of drug resistance. No new classes of malaria treatment will be available within at least 10 years making it imperative to ensure the highest standards of treatment and care with the existing drug regimen.

The failure to improve treatment standards for malaria exposes the deficiencies in drug regulation policies in many poor countries. Yet instead of focusing on better policing and ensuring higher standards of imported drugs, industrial policies in many malarial countries favor local production of malaria medicines. These policies, often supported by donor nations, will further burden the regulatory agencies in malaria countries. There is little evidence that local production of medicines produces cheaper, high quality drugs.

TARGETING BEST-KNOWN DISEASES

HIV/AIDS and bird flu treatments are also being jeopardized. In a 2004 study, one researcher discovered counterfeit antiretrovirals (stavudine-lamivudine-nevirapine and lamivudine-zidovudine) in central Africa. This is alarming because the previously effective first-line therapy for treating HIV could soon be rendered defunct as the virus develops resistance. The bird flu scare led to an increased demand for the antiviral drug Tamiflu, one of the proven remedies for the disease. Soon thereafter, fake versions of the drug were flooding the Internet.

Developing countries are not only markets for counterfeit drugs—they also produce the fakes, according to a report from the International Policy Network (IPN). The chief culprits are Asian countries like China and India, where oversight is weakest. According to figures cited in the British Medical Journal, China had 500 illegal medicine factories in 2001; in the same year, the *San Francisco Examiner* reported that the Chinese government closed 1,300 factories while investigating 480,000 cases of counterfeit drugs. According to the IPN report, about 15,000 manufacturers of copies operate in India, and while the majority are legitimate (even if their drugs are substandard), "a small minority are 'fly-by-night' operations that do not comply with proper regulatory standards." Most of the counterfeit medicines in Nigeria, for example, originate in India, which led Nigerian authorities to threaten to ban the import of all drugs from India in 2003. With an influx of legitimate Chinese investment in Africa, however, informed sources say that China may soon take the lead in this odious trade. The manufacture of fake medicines also flourishes in Latin American countries like Argentina, Brazil, Mexico, and Venezuela.

The production of counterfeit medicine often occurs through a multi-national chain of production and sale that originates in countries that either do not recognize or loosely enforce patent laws, where the drugs can be synthesized or their component parts bought. A copy manufacturer operating in Argentina, Greece, or Mexico purchases the ingredients from a country such as India or Thailand, then presses the tablets or makes the pills and prints counterfeit labels.

Wilfrid Roge, a former French Customs official who is now director of corporate economic security at the French pharmaceutical company Sanofi-Aventis, describes a typical path for counterfeits:

> "The products are transported to free trade zones in Dubai in the Middle East and are exported to Latin American countries like Panama. The products are then re-exported to North America and Europe through the United Kingdom and some north European countries."

The fake drugs eventually make their way through several cut-rate brokers to a pharmaceutical distributor.

These findings suggest that massive amounts of fake drugs are circulating in drug distribution chains. Even more worrisome, many patients are taking incorrect doses or compositions of drugs—with potentially lethal outcomes.

CASHING IN ON DEATH

In studies all over the world, counterfeit medicines, which contain little or no active ingredients, have no therapeutic benefits to patients. During the Niger meningitis epidemic of 1995, for example, 2,500 people died as a result of fake vaccines. In Haiti, Nigeria, Bangladesh, India, and Argentina, throughout the 1990s, more than 500 patients (mostly children) died after ingesting diethylene glycol (a chemical commonly used as antifreeze) offered as paracetamol syrup. Today, due in part to lax regulatory standards in China, we are seeing contaminated toothpaste from China containing the same ingredient.

WHO estimates that 1 million deaths occur from malaria every year. It is logical to conclude that this chilling estimate could be significantly reduced if the medicines available were effective, of good quality, and used correctly. WHO suggests that an astonishing 200,000 malaria deaths per year would be prevented absent fakes and poorly prescribed medicines. In 1999, at least 30 people died in Cambodia after taking counterfeit antimalarials prepared with sulphadoxine-pyrimethamine (an older, less effective antimalarial), which were marketed as the more advanced artesunate. A study conducted in Southeast Asia in 2001 revealed that 38 percent of 104 antimalarial drugs on sale in pharmacies did not contain any active ingredients and had led to several preventable deaths.

Perhaps one of the most worrying implications of the counterfeit boom is the acceleration of new, drug-resistant pathogens, parasites, and bacteria. The IPN report found this especially true of malaria and HIV/AIDS. Scientists have begun to observe resistant strains of bird flu, which could indicate that fakes are already penetrating the market for bird flu drugs. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) says that "drug resistance resulting from the use of counterfeit medicines is among key factors contributing to the upsurge of major infectious diseases in developing countries."

Aside from their hefty death toll, counterfeit drugs undermine incentives to invest in further research and development. The use of fake drugs also undermines confidence in health-care systems, health professionals, pharmaceutical manufacturers, and distributors. It deprives pharmaceutical companies of significant financial resources and places financial burdens on patients and governments with two major consequences: money is wasted on drugs that do not work, and additional funds must be spent on purchasing genuine products to deal with the ensuing devastation that toxic or under-strength products cause. This is particularly damaging in developing countries, where disposable income for health care is significantly constrained.

FIGHTING COUNTERFEITING DRUGS

Since its inception in 1946, WHO has often attempted to quell the spread of counterfeit drugs. Article 2 of the WHO Constitution establishes its obligation to set standards for pharmaceutical products. WHO initiated programs for the prevention and detection of counterfeit drugs, and in 1982 established a Counterfeit Drug Database. In 1992, WHO joined forces with IFPMA to settle on a working definition of a counterfeit drug. More recently, in 2000, WHO convened a working group on drug quality and counterfeiting. Made up of WHO officials and organizations representing patients, pharmacists, and medical professionals, the group hopes to raise awareness about the problem of counterfeiting while promoting effective regulatory safeguards to ensure that patients are protected from the hazardous effects of these medications. WHO is also promoting its International Medical Products Anti-Counterfeiting Taskforce, which is slowly mobilizing resources on a multilateral basis.

At the national level, some countries are taking steps to tackle this problem. Nigeria, which has a major problem with counterfeits, issues bulletins and maintains a Web site with information on counterfeit drugs and food to educate consumers. In 1996, the Philippines enacted a law permitting random sampling and monitoring of drug quality in pharmacies and hospitals and punishment of offenders with long prison sentences or hefty fines. The government in China, where many products are fraudulently manufactured, has taken the drastic step of sentencing an official formerly in charge of food and drug safety, Zheng Xiaoyu, to death for accepting bribes to approve counterfeit products. More punitive sentencing for those peddling fake drugs is certainly warranted, but it is only part of the solution. According to the legal literature, increasing the potential punitive cost (judicial sentences) of illegal activity often does not lower the activity significantly, but rather just increases the level of brutality involved. Stricter penalties must be combined with increased monitoring activity by technically qualified laboratories and concerted policing.

FIGHTING SUBSTANDARD DRUGS

Although WHO has done much to prevent the spread of fake drugs, it has actually encouraged the use of substandard drugs through the promotion of products it classifies as generics—but whose quality has not been verified by a stringent regulatory authority. As widely documented, this has been a significant problem for HIV drugs. Unfortunately, the Global Fund to Fight AIDS, Tuberculosis and Malaria has exacerbated the problem by listing generic drugs on its approved antimalarial compliance list that have not demonstrated bioequivalence therapies by registering with a competent agency. Sources inform us that nearly 20 percent of total purchases by the Global Fund—well over 450 transactions—are for non-approved drugs. European and Indian companies have also exploited loopholes in domestic legislation, which have allowed them to copy drugs for export without undertaking significant quality testing. Belgium and Italy in particular have allowed drugs produced in their countries to compete for Global Fund awards without having them fully tested.

It is uncertain how damaging substandard, pseudo-generic drugs may be for patient safety. Their use—and hence impact—is set to grow even faster than the market for fake drugs. This is disquieting, since the Global Fund does not see this as a problem. It continues to use funds from the Bill and Melinda Gates Foundation and the G8 countries to purchase such drugs. The Global Fund mistakenly assumes that because the drugs are cheaper, more lives will be saved, which is only true if the copies are bioequivalent to the originals. Meanwhile, the Fund continues to show antipathy toward the research-based pharmaceutical industry. The recent Board decision to increase access to antimalarials of unproven quality was the desire to prevent Novartis, the producer of Coartem, the best drug on the market, from increasing its dominance, even though Novartis sells the drug at cost.

When the new head of the Global Fund was asked about this issue in Washington in May 2007, he brushed it off. Only when tragedy strikes will action be taken. Action is vital because substandard drugs can be more dangerous than fakes—especially at the population level. Since they contain active ingredients, but at sub-lethal levels for the bacteria/parasite, they breed resistance.

Approval of poor copy drugs also provides cover for the broader acceptance of total fakes. When doctors and patients are inundated with new copy drugs, it is more difficult for doctors to discern total fakes, making drug policing more complicated and expensive.

LOOKING AHEAD

The problem of counterfeiting requires a concerted effort from all stakeholders. As one top health official from the Philippines noted,

> "The fight [against counterfeit medicines] is a cooperative undertaking." As the IPN paper notes, to contain the global counterfeiting scourge, it is crucial "to address those lacunae of governance which allow LDC counterfeiters to ply their trade with relative impunity."

Most importantly, it is essential that intellectual property rights and the rule of law be upheld in the countries where the majority of these drugs are produced. In South American countries, the penalty for illicit cocaine and heroin dealing is 15 years of jail time. The penalty for the production and sale of fake drugs is only 6 months; the perpetrator may be out on bail in only days. These sentencing incongruities should be rectified. Stiff penalties are needed because counterfeiting offers high profits, with comparatively low risks. In 2003, an expert committee in India recommended that the maximum penalty for the sale or manufacture of fake medicines be changed from life imprisonment to the death penalty and that the minimum prison sentence for these offenses be increased from 5 to 10 years. But as noted above, increasing sentencing without massively increasing policing will have little impact on the fake drug market.

Promoting generics as an alternative to tackling drug counterfeiting is not a viable option unless the recognized international standards—including the bioequivalence requirement—are in place to ensure the quality of product. Unless such standards are set, aid agencies will continue to exacerbate and tolerate bad medicine in the market.

SUMMARY

Counterfeit and substandard medicines are an insidious threat to the United States and to global health more broadly, and the risks they pose have been largely underestimated to date. Counterfeits containing no active ingredient will fail to cure disease; those with wrong ingredients may cause mental and physical damage—and even death. Counterfeits containing insufficient active ingredients breed resistance,

which can make authentic drugs useless. No area of the world is unaffected, as exposed by the recent deaths in the United States from tainted heparin. Mounting evidence shows that the problem is disproportionately severe in developing and emerging-market countries, which also have the highest burden of infectious diseases. National governments have the primary responsibility—both in stopping criminal manufacturing and distribution and in protecting their citizens from counterfeit products. The Food & Drug Administration (FDA) is highly active in fulfilling this responsibility, but this is not true in many other countries in the world. Multilateral organizations such as the World Health Organization (WHO), the World Customs Organization (WCO), and the International Criminal Police Organization (Interpol) must do more to expose the problem and help countries tighten regulatory controls. Companies affected by counterfeiting in developing countries are expending private resources to perform roles which should be carried out by police and regulators, including assisting multilateral organizations in building capacity among local customs and regulatory officials.

RESPONSES TO QUESTIONS OF SENATORS KENNEDY, ENZI, BURR, AND BROWN BY GERALD MIGLIACCIO

QUESTIONS OF SENATOR KENNEDY

Question 1. Your testimony confirmed my impression that responsible brand and generic companies have robust systems to evaluate and audit the companies from whom they source drug ingredients. I think it's pretty clear, however, that not all companies do what Pfizer and other responsible companies do. How wide spread do you believe these practices are?

Answer 1. It is difficult to give an accurate estimate of the percentage of industry that follows similar practice. Since my close association is with PhRMA companies, I can say that most have robust systems. However, I cannot give an informed answer for other industry segments.

Question 2. I believe practices on sourcing ingredients, including requiring drug companies to audit their suppliers, should be requirements that FDA should evaluate and enforce. Do you agree?

Answer 2. 21 CFR 211 and the FDA Quality Systems Guidance clearly require the Quality Unit to oversee activities conducted under contract by third parties. I agree that evaluation of a drug company's quality system, specifically in the area of management of suppliers and contractors, should be an area of strong focus during FDA inspections.

Question 3. What do you think of Bill Hubbard's suggestion that we improve the tests for impurities and contaminants in drug ingredients?

Answer 3. My 29 years of experience in the pharmaceutical industry have convinced me that it is not possible to test quality into a product. We must rely on quality systems to assure quality. We develop analytical testing methods to measure the purity and potency of active ingredients and drug products. These methods are designed to detect known process-related substances such as reaction byproducts, residual starting materials, residual solvents, degradation products, and other process-related impurities. No analytical method is capable of detecting all potential adulterants in an active ingredient or drug product. Furthermore, since testing is destructive, we can only test a very small portion of a batch. The quantity tested is statistically valid and more than adequate for measuring attributes that are uniform throughout the product, but it is possible that intentional adulteration would not be found to be uniformly distributed. In the end, excessive testing will provide a false sense of security to the American public.

QUESTIONS OF SENATOR ENZI

Question 1. I agree with you when you say that no amount of testing or inspection can ensure quality and safety. But I do think that product testing and facility inspection are still very important, as we've seen with the heparin incident. Could you go into more detail about the role that testing plays in safety?

Answer 1. Statistical sampling and testing does provide assurance that an active ingredient or drug product meets the requirements for potency and purity established by FDA to ensure safety and efficacy. The testing methods used are designed to measure the active substance to determine potency, usually against a reference standard of the ingredient. In addition, purity methods are employed that are designed to detect known process-related substances such as reaction byproducts, residual starting materials, residual solvents, degradation products, and other process-related impurities. The chemical characteristics of the active substance and po-

tential impurities heavily influence the design of the analytical methods. Contaminants or adulterants with similar chemical characteristics may also be detected with the same methods used for potency and purity. However, contaminants and adulterants with different chemical characteristics may not be detected with these methods. There is no single method that is capable of detecting all potential contaminants or adulterants in every active ingredient and drug product.

Question 2. Can you discuss some of the differences, particularly with respect to safety and quality, between sourcing ingredients from other countries, as Pfizer does, and the proposals to permit commercial importation of drugs from foreign countries?

Answer 2. When Pfizer imports a pharmaceutical product into the United States, that material is being imported from an FDA-approved site and with a supply change that is managed by Pfizer. When an individual or wholesaler imports material, there is no guarantee that the material is coming from an FDA-approved source, and the supply chain is not secure. The product is essentially unprotected as it passes through the supply chain. Importation facilitated by parallel trade provisions in the EU has led to rampant counterfeiting. Counterfeit Pfizer products have been confirmed in 21 of the 27 EU member countries. Counterfeit products have also been confirmed in the legitimate supply chain (on pharmacy shelves and dispensed to patients) in at least 3 EU member states. This issue is not limited to Pfizer; Lilly, Astra Zeneca and Bristol Myers Squibb counterfeit products have also been detected in the EU. According to the WHO, between 2001 and 2005, there were 27 instances in which counterfeit medicines breached the legitimate supply chain in the EU.

QUESTIONS OF SENATOR BURR

Question 1. There has been some discussion at this hearing about why drug companies contract with manufacturers in foreign countries instead of locating all manufacturing in the United States. You mentioned that some rationale is cost-based, which I understand. If Pfizer was forced to locate all manufacturing of all product ingredients and finished products in the United States, would you end up having to charge more for the finished product? Given some individuals' intense concern over high drug prices, I would think Congress would not want to do anything that would further drive up drug prices.

Answer 1. There are various factors which result in some products for the U.S. market being manufactured outside the United States. The more difficult operating environment and the slower growth rate in the industry has led companies to consolidate their global operations; seeking the most cost-effective locations to produce these products. This has led to the utilization of their newer facilities available outside the United States and/or the minimization of capital investment and operating costs. In addition, several countries have created significant industrial incentive programs which make it more attractive for companies to operate there. They have also created strong educational systems which produce very capable engineers and scientists that are made available to industry at a competitive cost. Companies weigh these competitive factors in determining where to manufacture.

[Whereupon, at 11:02 a.m. the hearing was adjourned.]

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