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RECENT DEVELOPMENTS WHICH MAY IMPACT CONSUMER ACCESS TO, AND DEMAND FOR, PHARMACEUTICALS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

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RECENT DEVELOPMENTS WHICH MAY IMPACT CONSUMER ACCESS TO, AND DEMAND FOR, PHARMACEUTICALS

WEDNESDAY, JUNE 13, 2001

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 2322 Rayburn House Office Building, Hon. Michael Bilirakis (chairman) presiding.

Members present: Representatives Bilirakis, Greenwood, Deal, Burr, Norwood, Bryant, Ehrlich, Tauzin (ex officio), Brown, Waxman, Strickland, Capps, Towns, Pallone, Deutsch, Stupak, and Green.

Staff present: Brent Del Monte, majority counsel; Marc Wheat, majority counsel; Kristi Gillis, legislative clerk; and John Ford, minority counsel.

Mr. BILIRAKIS. Good morning. This hearing will now come to order.

Today the subcommittee will consider three matters within the jurisdiction of the Food and Drug Administration which impact the demand for, and the price of, pharmaceuticals.

Congress is actively seeking to improve access to affordable prescription drugs for all Americans, and particularly our seniors. As we debate various proposals, we cannot ignore the impact of Federal food and drug laws on the availability and affordability of drugs. Today, we will focus on three specific areas which have received a lot of attention recently; access to generic drugs; the authority of the FDA to switch drugs from prescription to over-the-counter status despite a manufacturer's objections; and direct-to-consumer broadcast advertising.

At our recent Food and Drug Administration Modernization hearing I mentioned my intent to examine issues related to generic drugs. And that is one of the purposes of today's hearing. Generic drugs account for nearly half of all prescriptions filled, and yet they amount to less than 20 percent of pharmaceutical costs. Generics obviously save consumers billions of dollars per year, and we should carefully consider their role as we work to develop a Medicare prescription drug benefit.

I am particularly interested in learning more about the science of generics. For instance, how closely must a generic scientifically resemble the innovator drug for it to receive FDA approval? I un-

derstand that the scientific standard for generic approval is bioequivalence, but what exactly does that mean?

Also, do consumers understand and feel comfortable with, generic drugs and their role in the modern marketplace? In addition, I'm interested to learn why, on average, it takes the FDA longer to approve generic drugs than it does for new drug applications.

Of course, we can't lose sight of the fact that without a healthy, vibrant brand-name pharmaceutical industry, there would be no generic drugs. And I'd like to commend our colleague, Mr. Waxman, for his work as co-author of the Hatch-Waxman Act, or as we like to call on this side, the Waxman-Hatch Act, which increased consumer access to generic drugs, while strengthening patent protections for new chemical entities. The Act has proven quite successful for the past 17 years. Both the brand name pharmaceutical and generic industries have thrived, and consumers have benefited greatly by access to both new therapies and to cheaper copies of old therapies.

That being said, concerns have been raised about provisions of the Waxman-Hatch Act which may lead to anti-competitive behavior. The Federal Trade Commission is presently conducting a yearlong review to consider this matter. Our witnesses today will shed light on the continued utility of the automatic 30-month stay on FDA approval during patent challenges, as well as how the 180-day generic exclusivity provision is working.

While I know that some of my colleagues may wish to consider additional generic issues, we simply do not have the time today to consider all of these matters. Thus, I hope we can focus on the role of generic pharmaceuticals and not delve into other areas today.

The subcommittee will also consider the authority of the FDA to force a drug to be switched from prescription to over-the-counter status despite the objection of the drug's manufacturer. We are not looking at whether FDA should switch specific drugs, and I want to make that clear. We're not intending to look at whether the FDA should switch specific drugs, which have been in the news recently, but rather whether FDA can under the law make the switch. And if they can, what are the policy impacts of such action?

Last, we'll hear from witnesses who will discuss the impact of direct-to-consumer broadcast advertising on consumers. In 1997, the FDA changed the guidelines for broadcast drug ads, and since then this advertising has increased, as we know, dramatically. While the advertising has mostly focused on the top selling drugs, it has also served to better inform consumers. Today, this subcommittee will consider the full impact of broadcast drug advertising on consumers.

And I now yield with pleasure to Mr. Brown for an opening statement.

[The prepared statement of Hon. Michael Bilirakis follows:]

PREPARED STATEMENT OF HON. MICHAEL BILIRAKIS, CHAIRMAN, SUBCOMMITTEE ON HEALTH

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I will now yield to Mr. Brown for an opening statement.

Mr. BROWN. Thank you, Mr. Chairman, very much for holding today's hearings. I want to thank Janet Woodcock and also Bruce Downey and other witnesses for joining us this morning.

We're looking, as the chairman said, at three prescription drug issues that are in some ways very different but which derive their significance in part from the same basic concern; they have a significant impact on prescription drug costs in the United States.

Our objective in looking at these issues is not to dismantle legitimate incentives and rewards for innovative new drugs and biologics. This subcommittee, this committee, this Congress have a pressing responsibility to understand the factors driving the dramatic increase in prescription drug spending and explore what steps w should take to minimize wasted spending.

Inflated drug prices rob seniors of dollars they need for basic necessities; they fuel double digit increases in health insurance premiums; they drive up the cost of public programs; they accelerate the erosion of employer sponsored coverage. Responsibility for establishing a prescription drug benefit under Medicare rests squarely on our shoulders and we simply can't afford to waste a single tax dollar on artificially inflated drug prices.

I want to start with generic drugs and focus on access. I want to commend my colleague Mr. Pallone for introducing the Generic Drugs Access Act which tackles bio-equivalency disputes at the local and State levels. And I want to take this opportunity to discuss the Greater Access to Affordable Pharmaceuticals or GAAP Act legislation which I introduced with Republican Jo Ann Emerson. This is the House version of the Mc-Cain Shumer Bill.

The explicit goal of the Brown-Emerson, Shumer-McCain Bill is to restore the original intent of the 1984 Waxman-Hatch Act, the goal of which was to promote generic competition while continuing to encourage drug research and development. At friends at PhRMA are going to make other claims about this bill. I understand they've already visited some of my subcommittee colleagues.

PhRMA claims that the GAAP Bill undercuts the incentives Bill into Waxman-Hatch to reward research and development. In fact, the bill doesn't touch the provision of Waxman-Hatch that were intended to reward innovation.

PhRMA claims it would reduce the patent life of brand name drugs. This bill would have no effect on the statutory patent life of brand name drugs.

You'll hear it lowers the bio-equivalency standards used to ensure that a generic drug is identical to and therefore is safe and as effective as it's brand name counterpart. In fact, the bill codifies three standards that the FDA already uses to determine bio-equivalency. Putting the force of law behind these firmly established standards is one way to fend off endless and inevitably frivolous lawsuits intended to delay generic drug approvals.

With all due respect to PhRMA, it makes as little sense to defer to them on bio-equivalency standards as it does to defer to the generic drug industry on bio-equivalency standards. Both parties have a vested interest in the outcome of bio-equivalence analysis. It's kind of like trusting two oil men to come up with a balanced global warming policy. Never mind on that.

So what would the GAAP Bill do?

Mr. Burr's not here, but I didn't want to disappoint him so he could say that this hearing is partisan, Mr. Chairman.

So what would the GAAP Bill do? It would keep brand name drug companies from misusing Waxman-Hatch to block legitimate generic competition. Brand name companies cut deals with the first generic challenger to keep it off the market because they know that as Waxman-Hatch is currently written, no generic can enter the market if the first one doesn't.

Brand name companies file last minute patents on their drugs because they know that by suing a generic for patent infringement they can automatically delay FDA approval by 30 months. And brand name companies cut deals with generics to keep them off the market.

They claim we should protect their right to "settle court cases.' What they need to remember, Mr. Chairman, is that they're settling their case with one generic competitor, not with every potential generic competitor and every American consumer. We should not all have to pay to reduce their time in court.

I look forward to discussing other provisions of the bill and other generic drug issues, including the chronic under funding of the Office of Generic Drugs when we hear from our witnesses later.

I want to briefly touch on DTC advertising and over-the-counter drugs. In the terms of direct-to-consumer advertising there clearly are First Amendment implications. But on behalf of consumers, FDA requires DTC advertising to strike a balance between promoting and explaining the limitations and risks associated with prescription drugs. They're also fairly explicit truth in advertising laws.

Tuesday's article you may have seen in the Washington Post regarding once-a-week Prozac. There are questions about whether DTC ads fairly represent their products. It's certain they don't highlight the relative price of their product and how that relates to its efficacy. My guess is that if consumers had the full picture, DTC ads would be much less inflationary than they are today.

Two thousand increases in sales of just 23 drugs promoted directly to consumers accounted for half of the $21 billion increase in pharmaceuticals at retail spending.

In terms of over-the-counter drugs because Congress had the authority to modify the relevant law, it's important to assess whether FDA has legal authority to consider the safety of an over-the-counter determination based on an outside petition. But the reason the WellPoint case is so important is because it's promoted us to ask the critical question how should these determinations be initiated. Is it a conflict of interest when an insurer initiates this change? Is it a conflict of interest when a drug company initiates this change, which coincidentally they do not do until their patent is expired?

It's in the public's best interest to reevaluate the current process and answer these questions. Prescription drugs save lives, they prevent illness, they reduce the hardship of disabilities; that's why it's important to maintain incentives for prescription drug research and development. That's what this committee needs to do. But it's also why it's important to eliminate any kinks in the current system that artificially inflate prescriptions drug prices. Too much is at stake, Mr. Chairman, to look the other way.

Thank you.

Mr. BILIRAKIS. The Chair yields to Dr. Norwood for an opening statement and would request that we try to stay within the 5 minute rule, if we possibly could.

Dr. Norwood.

Mr. NORWOOD. Thank you very much, Mr. Chairman. And I am grateful to you for this very important, interesting and hopefully bipartisan hearing.

I don't really think that I can add much to your opening statement. It said it all pretty well, other than to thank the witnesses, Dr. Woodcock and others, for being here.

In a sense of timing, I'll yield back my time so we can hear from the witnesses.

Mr. BILIRAKIS. The Chair thanks the gentleman.

Mr. Pallone for an opening statement?

Mr. PALLONE. Thank you, Mr. Chairman. I want to thank you and Mr. Brown for holding this hearing on these issues, particularly the generic drug issue which is very important to me.

As you know, the high cost of prescription drugs is one of the most pressing health care issues confronting our country's senior citizens, employers, managed care plans, State and Federal drug programs. Although controlling drug costs is not an easy task, generic competition can have a dramatic impact on reducing pharmaceutical costs, and I strongly support necessary changes to Waxman-Hatch that would allow timely access and availability of generic drugs once the patent on brand name drugs expires.

The inclusion of generic alternatives in the marketplace is great for consumers, employers and government purchasers because generic competition provides access to less expensive, therapeutically equivalent generic versions of brand name drugs. Brand name companies have been proficient in manipulating the Waxman-Hatch law and launching aggressive campaigns to block or delay generic alternatives from reaching the market.

The intent of Waxman-Hatch was to provide a balance between brand name drugs and generic drugs in the marketplace. But currently the scales are tipped heavily in favor of the brand name companies. This is clear from the number of pieces of legislation that have successfully extend the patents on blockbuster drugs and reaped extraordinary profits for these brand name companies.

The balance in the marketplace needs to be restored for the benefit of the consumer and an examination of Waxman-Hatch can be done, I think, best through the GAAP Bill which Mr. Brown has sponsored and which he mentioned, the Greater Access to Affordable Pharmaceuticals Act. I call it GAAP.

I would like to talk a little bit about how the big name drug companies have several frequently used methods to delay generic competition. One of their favorite tactics is to make insignificant changes to their products and secure new patents just as the patent on the original product is set to expire. New patents are granted by the Patent Office for frivolous and invalid reasons, such as changing the color of the bottle, however you know the problem is that once the new patent is presented, the current law protects these brand name companies by prohibiting a generic from going on the market for 30 months.

Another favorite method used by the brand name industry to manipulate the intent of Hatch-Waxman—oh, did I say Hatch-Waxman, I'm sorry. Waxman-Hatch. Is inserting patent extensions into legislative vehicles. In the interest of keeping pharmaceutical drug costs down, Congress should reject attempts by the brand name industry to extend patents on profitable drugs by finding sponsors to inconspicuously insert these patent extensions into various legislative vehicles.

And last, the misuse of citizen petitions by brand companies is widely used to delay the approval of generic drugs. Often times, brand name companies file a citizen petition with the FDA as a

method of blocking the regulatory process, and as a result brand name companies are afforded months or even years of monopoly. Agency officials reviewing these petitions are administratively challenged, and this leaves the review and approval of generic drugs on the back burner. Just another example of where legislative changes could prevent a citizen petition from delaying the approval of a generic drug that would ensure patient safety and improve access, and of course the GAAP Bill seeks to accomplish that.

I don't want to keep talking about all these tactics, but the bottom line is that the brand name industry does delay generic drugs from entering the marketplace. It's widespread, it's well known and I think we have to open up Waxman-Hatch to find avenues that would stop these delays.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Waxman, for an opening statement.

Mr. WAXMAN. Thank you very much, Mr. Chairman.

By any definition, pharmaceuticals are important to Americans. Some people place hope in research toward cures, some people are struggling to afford the treatments that are already known. This is the balance, progress and access. Neither make sense without the other. It is unfair and wasteful to develop new products that sick people can't afford. It is pointless to get easy access to products that don't help.

This is a balancing act that I know well. I've been working on it for almost 20 years now. I'm pleased and proud that the legislation that bears my name has been so uniformly regarded as successful in its twin goals.

I'm also always reluctant to open it up to amendment, whether it be for ad hoc patent extensions or response to individual court ruling, or for fine tuning to address market changes. The road to imbalance is paved with good intentions.

But while I'm cautious about opening it up, I will not stand by as a system is abused. Over the past year I've been very troubled by reports of collusive arrangements between brand name and generic companies of near frivolous patent infringement and of late additions of patents unrelated to the basic functioning of the drug. I only wish that the manufacturers who benefit from the system were as cautious about throwing it into imbalance as I am.

Such clear abuses invite legislative response, and while I'm cautious about amending the law, I will not let my caution be abused.

I look forward to the testimony and questioning today of those witnesses that are before us, and I hope I'll have other opportunities to explore these very complicated but truly vital issues further.

Mr. Chairman, just on a diplomatic note of clarification, both Waxman-Hatch and Hatch-Waxman are acceptable usages. In fact, if you did a quick computer search it would show that both are widely used.

It's been the tradition that I refer to this law as the Hatch-Waxman Act and Senator Hatch call it the Waxman-Hatch Act just out of courtesy to each other and to the other party.

Again, this is another one of those balancing acts. But I want to point out that it is not acceptable to call it the "Wax-Hatchman' or

the "Hatchman-Wax Act.' Any other use of our names in any order is quite acceptable.

Mr. BILIRAKIS. I would say, Mr. Chairman, if I might still refer to you as such, that we are not—we personally are not bound by that tradition. You may be bound and Mr. Hatch may be bound, but not us. So it's still the Waxman-Hatch Act on this side of the Capitol.

Mr. Stupak for an opening statement.

Mr. STUPAK. Well, thank you, Mr. Chairman. And thanks for holding this very important hearing on recent developments in prescription industry. I believe it's the duty of this subcommittee to monitor and take necessary action to approve our Nation's healthcare system, of which prescriptions drugs play an increasingly large role.

Here are the indisputable facts. Prescription drug spending has increased by $20.8 billion or 18.8 percent just last year. Seniors, one-third of whom lack prescription drug coverage, received a 2.4 cost of living increase in their Social Security benefit last year.

Less than half of the prescription drug cost inflation is linked to the increased use of prescription drugs. The rest is attributable to higher prices, annual price increases and shifts from lower costs to higher cost drugs.

The hearing today focuses on three major issues facing the American in today's health market: direct-to-consumer advertising, over-the-counter drugs, and generic drug issues. Each of these three issues are substantial in their own right.

The speed of generic drugs into the marketplace is one area in which I am particularly interested. In 1994 the Waxman-Hatch Act was passed during a time when the drug approval process was slow. Now, 17 years later, it's the norm rather than the exception to have a drug approved in 12 months. This change in the FDA approval process should also necessitate a change in the speed in which the FDA is able to approve generic drugs. Pharmaceutical companies, while indisputably delivering some excellent products, are using the loopholes in the Waxman-Hatch Act to extend their strong hold on their products and, thus, increase their profits.

Another area of particular concern to me is the direct-to-consumer advertising. While this is seen by many as a necessary way to gain greater knowledge about drugs and healthcare in general, I'm alarmed at the incredible amounts of money being spent on direct-to-consumer advertising, as well as the fact that the drug companies are responsible for outlining the risk of their drugs with little oversight from the FDA. Many drug companies are failing to outline the risk to consumers.

The goal of this hearing is to find the best way to lower drug prices for consumer while at the same time ensuring consumer safety, and it's a goal everyone can support.

The three issues we will discuss are seen as possible areas we can improve upon to lower drug prices, better drugs and improve healthcare systems.

Mr. Chairman, I sincerely hope this hearing resolves questions I and others have on these issues. And thank you again for holding this hearing.

Mr. BILIRAKIS. And I thank the gentleman.

Mr. Green for an opening.

Mr. GREEN. Thank you, Mr. Chairman, for holding this hearing on consumer access to and demands for pharmaceuticals. It's the interest of all Americans, but especially relevant to our committee, as we consider ways to provide an affordable Medicare prescription drug benefit for seniors. According to the National Institute of Health Management, costs of prescription drugs has risen dramatically over the last 15 years.

Last year alone, we saw a 19 percent increase in spending on outpatient pharmaceuticals. Increases in sales of just 23 drugs were responsible for half of this increase, including Vioxx, Lipitor, Prevacid and Celebrex. It shouldn't be a surprise to anyone that these drugs are among the most popular, consumers are bombarded with advertisements for these medications every time they open a magazine, turn on the television or surf the Internet. The proliferation of direct-to-consumer advertising has a strong effect on the consumer utilization of pharmaceuticals.

Consumers are taking a more activist role in their treatment. For the first time they're asking their physicians to prescribe a course of treatment including the pharmaceuticals that they see advertised.

Mr. Chairman, I believe it's important for consumers to be informed about their healthcare options and they should work their doctors for treatment. But it does concern me when we see marketing costs for pharmaceuticals almost equaling the research and development costs for pharmaceuticals.

The FDA's recent recommendation to make certain allergy medications available over-the-counter has sparked fierce debate on the FDA's right to make such a change absent the consent of the sponsor. There are questions about how such a move would impact consumer's access to such drugs, who would bear the economic burden of the shift and whether such a move would create a disincentive for the innovation.

Finally, consumer's access for affordable pharmaceuticals is greatly enhanced by the availability of generic alternatives. The Drug Price Competition and Patent Term Restoration Act of 1984, also know as the Waxman-Hatch Act, was a compromise bill which successfully increased the availability of generic alternatives and at the same time protecting their patents for innovation or innovator companies. At the time it passed, this legislation represented a compromise approach to meet the needs of both the innovator drug companies and generic companies. The balance, though, has shifted in recent years as loopholes in the law have created the opportunity for abuse in the system.

For example, innovator companies often file a number of patents, staggering patent applications to extend their patent protections and, thus, their exclusivity. They're gaming the system and I don't think Congress should continue them to allow to do that. By staggering the patents, this loophole creates the possibility for innovator companies to receive multiple and unlimited stays for a single drug. This patent stacking results in lengthy delays and excessive litigation before the problems are resolved and alternatives can reach the market.

Additionally, these new patents are often for peripheral issues, such as the pharmaceutical's color, its labeling, or even are indication. These include minor changes, and that's why Congress should update the Waxman-Hatch Act.

I know my good friend from Ohio, Sherrod Brown has introduced legislation which would stem some of these abuses and level the playing field for the generic pharmaceuticals. While I've not cosponsored my colleague's bill, I grow more and more concerned that Congress must take action to close the loopholes that we've seen develop since 1984.

As we in Congress struggle to provide an affordable prescription benefit for seniors, we must look at all these issues.

I look forward to the testimony today. And I yield back my time, Mr. Chairman.

Mr. BILIRAKIS. I thank the gentleman.

Ms. Capps for an opening statement.

Ms. CAPPS. Thank you, Chairman Bilirakis. I'm pleased we could be here today to address this issue.

The news just this week of the cost of living compared with the exorbitant increases in medications, prescription medications, I think is further testimony to the fact that something's out of control. The prices have skyrocketed, and so it is high time that Congress take a long hard look at some of the factors influence the price of prescription drugs.

Today prescription medications are often the preferred, and sometimes the only method of treatment for many illnesses and diseases, but the cost in so many cases is a deterrent so that patients are not getting this often life saving treatment that they need. Therefore, we on this committee need to address this issue.

There are certainly no simple solutions. We will need to closely examine the various factors that effect drug pricing, such as competition and cost of development and distribution. Seventeen years ago Congress took a tremendous step in improving competition with the Waxman-Hatch Act. It has had a dramatic effect quadrupling the percentage of the market represented by the generic drugs while continuing to protect the right of patent holders and encouraging new drug development. But I'm concerned about reports of abuses by pharmaceutical companies of the protections and incentives that this law provides. These reported abuses could impede the access the generic drugs have to the market and to my constituents.

Claims have been made that brand name companies are using loopholes in the 30 month day and the 180 day market exclusivity provisions to indefinitely delay the production of generic drug competition. In light of these charges, it is time for us to look at improving the Act. As we take this up, we certainly must not discourage innovation and new ideas. There must continue to be strong incentives for companies to spend on research and development, but we cannot follow these incentives—we cannot allow these incentives to prevent our constituents from being able to afford the medications that they need.

The increased competition that generic drugs bring to the marketplace has saved purchasers $8 billion to $10 billion according to a 1998 CBO study. Clearly, this is important because if we are to

implement a real prescription drug benefit for our seniors, we are going to have to find ways to contain costs.

So I'm looking forward to hearing the panel's perspective on how we can do this, eager to hear their thoughts on direct-to-consumer advertising or DTC. DTC may have the potential to improve the public's understanding of their health needs and options, but I am concerned about the resources being spent here, resources that add to the cost of drugs and ultimately come from the consumer's pocket.

We cannot permit companies looking for a way to increase their profits to exploit their consumers, our constituents. And I also think we must make sure that any such advertising meets the strictest guidelines to protect American safety.

I want to thank Mr. Waxman for his years of leadership on this issue and recognize the leadership of Representatives Brown, Pallone, Eshoo and Dingell on these matters. They've worked hard to find ways for the public to have more access.

And I look forward to working with you, Mr. Chairman, to continue this work and improve our health system.

I yield back the balance of my time.

Mr. BILIRAKIS. The gentlelady's time has expired.

I'd like to very much to be able to get through the opening statements before we run over to vote.

Mr. Deal for an opening statement.

Mr. DEAL. I'll assist you, Mr. Chairman, by passing.

Mr. BILIRAKIS. I thought you might do that. Thank you.

Mr. Deutsch.

Mr. DEUTSCH. Thank you, Mr. Chairman. I thank the chairman and ranking members for calling this hearing.

Mr. Chairman, while all the issues we will hear about today are serious and deserving of attention, there's one aspect of this hearing that I think is particularly important to focus on today: Patent issues under Waxman-Hatch Act.

While direct-to-consumer advertising and over-the-counter switches may have some impact on the high cost of drugs, nothing contributes to the prices our constituents pay at the pharmacy like delaying generic entry into the market.

I hear everyday from constituents who are struggling with paying the high cost of drugs. I also frequently hear from the pharmaceutical industry giving me reasons why drugs are so expensive and why I should help to maintain these extraordinary prices. And while I agree that research into life saving therapies is a cost and necessary venture, we should address how brand name companies game the patent and Orange Book Listing, thereby inflating drug prices even further and delaying entry of low cost generics into the market.

We should also address the FDA's role in this system and failure to adequately ensure the validity of many patents.

I have seen and heard of numerous examples during my years in Congress of a generic drug set to go to market only to be delayed because a brand name company has filed an Orange Book Listing with the FDA stating that they deserve additional market exclusivity on an active ingredient because they've changed some part of the pill, it's shape, color or size.

And then another generic company is forced to delay entry of its product into the market until the new patent expires or they can successfully challenge the patent. Amazingly, FDA is a full partner in this process, simply listing patents in the Orange Book without regard to the value of the patent. That makes no sense to me since the FDA deals with patents on drugs, devices, cosmetics and other products every single day.

Recently Biovail, a brand drug company listed a patent in the Orange Book that they said applied to their drug Tiazac, which was about to lose its original patent coverage. During litigation FDA testified that it believed the new patent actually did not and could not apply to Tiazac. Additionally, the FDA testified that it was unilaterally prepared to delist the patent from the Orange Book. Nevertheless, after all this testimony the FDA turned around and sent a letter to Biovail telling the company that they would continue to list the patent as applying to Tiazac as long as Biovail sent a letter to them confirming the same.

Essentially the FDA said to Biovail help us help you lie to us. If that is what Congress intended in Waxman-Hatch Act 17 years ago, I doubt it.

The question we have before us is what do we do now? Frankly, I don't blame the brand companies for exploiting these loopholes. That's just plain business sense. It's now up to us in Congress to prevent this kind of abuse of the patent and Orange Book systems.

I fully support Ranking Member Brown's legislation, part of which requires brand name manufacturers to list all the drugs relevant to that and certify with the FDA that the list is complete and accurate. This bill also expedites the legal process for challenging late listed patents.

We may also want to look at limiting patents that can be listed in the Orange Book to the active ingredient and the first mode of use. Whatever we do, we need to ensure that FDA becomes a more willing partner in this process.

I'm interested to hear from the witnesses and what they have to say.

And I yield back the balance of my time.

Mr. BILIRAKIS. The Chair thanks the gentleman.

We will break now. The opening statements are hereby ended. The written opening statement of all members of the subcommittee are hereby made a part of the record without objection.

[Additional statements submitted for the record follow:]

PREPARED STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for holding today's timely hearing on recent developments which may have an impact on consumers' access to and demand for prescription drugs. These are complex issues, and we need to have a good grasp of them as we work together to craft a Medicare prescription drug benefit.

It was my pleasure to serve with you on the House Leadership's Prescription Drug Task Force in the last Congress and to see the plan we crafted win bipartisan approval by the House. I sought to serve on this task force because I strongly believe that no senior citizen should be forced to forego needed medication, take less than the prescribed dose, or go without other necessities in order to afford life-saving medications. Our nation leads the world in the development of new drugs that enable us to effectively treat diseases and conditions. But if people cannot afford to buy these drugs, their benefits are lost to many in our population.

Mr. Chairman, I am looking forward to working with you and my colleagues on both sides of the aisle and with the new Administration to craft a plan that can win the bipartisan support necessary to move quickly through Congress and be signed into law by President Bush. We cannot allow another Congress go by without providing relief to the millions of seniors without prescription drug coverage.

PREPARED STATEMENT OF HON. BARBARA CUBIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WYOMING

Pharmaceutical products have come a long way over the course of the past two decades, reaching new heights in innovation and research and development.

Because of that, many lives have been saved. Heaven forbid we should do anything to jeopardize that continued success in the future.

Since passage of the Hatch-Waxman Act in 1984, we have seen more generic drugs make their way into the market and into the hands of consumers.

In 1980, before Hatch-Waxman, CBO estimated that 13 % of prescriptions filled were generic; by 1998, generics comprised 58 % of total prescriptions. Those numbers tell us that Hatch-Waxman has played a pivotal role in making generic drugs more accessible to patients.

At the same time, Hatch-Waxman has helped foster research and development. Pharmaceutical companies have increased their R&D spending from $3.6 billion in 1984 to over $30 billion in 2001.

That is very encouraging, especially for those of us, presumably most, who depend on drugs everyday for quality of life.

Hatch-Waxman is not, however, without its controversies—namely when it comes to pharmaceutical patents. To the extent Hatch-Waxman has caused some grumblings in this area, we will soon discover through the course of this hearing today.

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

PREPARED STATEMENT OF HON. W.J. "BILLY" TAUZIN, CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE

Mr. Chairman: I'd like to begin by commending you for calling this very important, and timely, hearing today.

Our purpose today is to consider three important matters: Access to generic drugs, direct-to-consumer broadcast advertising, and the government's authority to switch prescription drugs to over-the-counter status over the objection of drug sponsors. These three issues directly impact our constituents who want the best quality pharmaceuticals at the lowest possible prices.

In 1984 the Congress passed the Hatch-Waxman, or as my friends on the other side of the aisle call it, the Waxman-Hatch Act. This Act did two primary things: it restored patent terms to innovators which had to navigate the lengthy FDA drug approval process prior to marketing, and it provided an expedited drug approval process for generic drugs. In my view, the 1984 Act has proven to be a resounding success. In 1984, the market share for generic drugs was less than 20%, and today that figure stands at nearly 50%. So consumers now have greater access to lower-priced therapies. At the same time, we've seen an explosion in innovator investment in research and development. Research-based pharmaceutical companies have increased their R&D spending from $3.6 billion in 1984 to over $30 billion today. Knowing that innovator drugs will face competition immediately upon patent expiration forces the innovators to do what they do best: innovate.

That being said, there are some who urge that the 1984 Act needs some fine-tuning; that certain loopholes have been abused, thus delaying consumer access to lower-cost generics. The primary focus of these comments concern the automatic 30 month stay on generic approval at FDA when the generic challenges an innovator patent as invalid or not infringed, and the 180 day generic exclusivity provision of the Act.

There have been a few recent, high profile examples of abuse of the 30 month stay provision. And while these few examples have led some to call for major revisions of Hatch-Waxman, I say let us keep things in perspective. While some reforms may be necessary, we cannot lose sight of the fact that between 1984 and January, 2001, 8,259 generic applications were filed with FDA, and only 478 generic applications, or 5.8% of the total, raised any patent issues. In essence, the 30 month stay is rarely a barrier to generic access to the market. That is not to say, however, that the

Congress must turn a blind eye if the stay acts as an artificial barrier to generic competition. These are issues we must consider today.

Further, we must explore how the 180 day generic exclusivity provision is working. I believe there should be incentives for generics to challenge weak patents. In 1984 it was thought that 180 days of generic exclusivity would ensure this. But the market place has changed dramatically since then. Now we see three, four, some times five generics lining up to challenge patents on blockbuster drugs, even though only the first generic to challenge is eligible for the exclusivity. Further, the courts have determined that to be eligible for the exclusivity all the generic has to do is file the challenge first, not successfully defend a patent infringement case. These developments raise many issues we need to explore: For example, should the exclusivity roll to subsequent challengers when the first challenger settles its case? Or, is the statutory incentive even necessary now, given the market incentives which lead to multiple generic applicants with no chance of exclusivity challenging patents?

Regarding direct-to-consumer, or DTC, broadcast advertising, I am especially interested in learning whether these ads lead to increased utilization of inappropriate therapies, educate consumers to seek therapies which lead to healthier lives, or maybe a bit of both. There has been a lot of anecdotal information on this subject, and I know that FDA is presently conducting a review of DTC's impact.

While increases in DTC broadcast advertising spending have coincided with increases in overall expenditures on pharmaceuticals, I think it is premature to draw a causal connection between the two, though the existence of a connection must be studied. There is information pointing to DTC broadcast ads having an overall positive impact. For instance, a 1999 FDA survey found that 27% of those who sought information from their doctors after seeing a DTC ad asked their physicians about a condition they had not discussed before. Further, a recent Prevention Magazine survey found that 76% of Americans believe DTC ads help them become more involved in their own health care. At the same time, there is no denying that the advertising is concentrated on a relatively short list of drugs. The most recent statistics show that about 12 drugs accounted for nearly half of all DTC broadcast spending. And it probably comes as no surprise that these drugs are some of the biggest sellers.

Last, the Subcommittee will focus on whether the FDA has the authority to switch a drug from prescription status to over-the-counter, or OTC, status over the objection of drug sponsors. This issue just recently came to the fore when one of our witnesses before us today, WellPoint, filed a citizens petition urging such a switch. The issue to me isn't whether the drugs at issue in the WellPoint petition are safe enough to be switched, but rather whether the FDA has the authority to make the switch without the consent of the sponsor.

For past decades, it was widely understood that the only way to sell an OTC drug was to either comply with a monograph, or to petition the FDA for a switch of your prescription drug through a new drug application. However, there is no denying that Section 503(b)(3) of the Code states that the "Secretary may by regulation remove drugs [from prescription status] when such requirements are not necessary for the protection of the public health." While this provision in the Code is a half-century old, it's plain meaning seems evident. I need to hear from our witnesses why my understanding of this provision may be misinformed, or whether I understand it correctly.

And if it turns out that the Secretary does have the authority under the Code to make the switch, we must explore what kind of process must be afforded to drug sponsors who object to the switch. Are they entitled to evidentiary hearings? Will they be forced to conduct label comprehension studies? Will the switch amount to a Constitutional taking? We should consider all of these issues at our hearing today.

Thanks again, Chairman Bilirakis, for considering these very important issues today. I look forward to the testimony of our witnesses.

PREPARED STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Thank you, Mr. Chairman. I share your interest in these issues which strike at the core of consumer access to prescription medicines. I'm concerned, however, that by dealing with all three in one hearing, we are giving them short shrift. Each of these issues raises numerous questions. So I hope this will be the first hearing for each.

That said, I'm looking forward to the testimony from today's witnesses. As the representative of California's 14th Congressional District, home to the largest con-

centration of biotech companies in the world, I have a keen interest in each of these issues.

I'm particularly interested in hearing from FDA on their recent decision to move three antihistamines from prescription status to over-the-counter. This has received quite a bit of attention recently and it raises numerous legal questions, not the least of which is whether FDA has the statutory and constitutional authority to take this kind of action over the objections of the drug manufacturer.

But even more important is the impact on consumers. Will safety be compromised and will the risk of this kind of unauthorized "switch" negatively impact future development of breakthrough medicines? These are just some of the questions this Committee and FDA must consider as we forge new ground on this issue.

I'm also keenly interested in the direct-to-consumer advertising issue. When FDA finalized its guidance in 1999, it opened the door and allowed drug companies to advertise their products—on TV, in magazines, even in newspapers. For the first time, doctors weren't the only ones holding the knowledge. Consumers were coming to their doctors armed with information and demanding a higher level of care.

Prior to these ads, prescription medicines were a mystery with names we couldn't pronounce and side effects we didn't even try to understand. Today, consumers know the drugs they're taking, any potential side effects, even how they interact with other drugs. Gone are the days when we simply accepted what our family doctor told us. We read, we surf the web and, yes, we listen to advertisements.

One of the issues before this Committee is whether the current system for direct-to-consumer advertising is providing consumers with *enough* information.

Finally, we cannot go home today without acknowledging that all these issues are tied to a larger policy debate which has plagued this Congress and the nation—the need for prescription drug coverage in Medicare. We're so wrapped up in trying to get at the pricing issue that we're failing to do the one thing that will provide relief—a Medicare drug benefit. We're missing the forest for the trees. Rather than spending time trying to shorten patent lives and switching drugs from prescription to over-the-counter—which may actually *increase* the prices for many beneficiaries—let's put our heads together and come up with a meaningful prescription drug benefit for every senior. The American people want it, they need it, and they deserve it. It's time we paid attention.

PREPARED STATEMENT OF HONO. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for scheduling this hearing. All three topics of this hearing, Over-the-Counter drugs (OTC) switching, Direct-to-Consumer (DTC) advertising, and the Waxman-Hatch Act are matters in which I have a long-standing interest. The pharmaceutical marketplace is of ever-increasing importance to citizens, and Committee attention to these matters has been lax for the past several years. We know that millions of Americans cannot afford, and therefore do not take, the drugs that they need. As a general matter, I will be curious to learn what our panel knows about the competitive nature of the pharmaceuticals market.

With respect to DTC advertising, I have long-standing concerns about commercialization of the doctor-patient relationship as it applies to prescription drugs. I agree that well done advertisements on public health issues can provide a substantial public health benefit. Ads on tobacco, sexually transmitted diseases, vaccines, domestic violence, drug abuse, and other causes of premature death and disease have worked. That is an entirely different matter than the case of a prescription drug product sponsor running an advertisement for its product. The latter case moves from the general message of urging people to take some action of benefit to their health to a related, yet distinct, effort to urge persons to consume a particular product. Are DTC ads improving the health of this country and, if so, how and to what extent?

There is no doubt in my mind that the Waxman-Hatch Act has saved consumers billions of dollars in prescription drug costs and, in doing so, has improved the health of millions of persons. That said, I wonder if this law any longer can realize its full potential as tens of billions of dollars of prescription drugs are scheduled to go off patent in the next several years. My point is that a very good law has acquired some tattered edges due to judicial decisions, administrative actions, and clever lawyering by brand name drug manufacturers. This law was enacted in 1984 and has not been revised since then. That is a long time in the life of any public policy, especially one that affects the disposition of many billions of dollars. I understand that our witnesses today will not discuss ideas for fundamental reform, but

will limit their remarks to proposals aimed at restoring the original balance of the Waxman-Hatch Act between product innovation and price competition.

Finally, we will hear two very different opinions on the issue of who can initiate the switch of a prescription drug to over-the-counter status. The arguments pro and con are intriguing and I look forward to the testimony.

Mr. Chairman, I hope this hearing is only the beginning of a substantial Subcommittee effort to address pharmaceutical market issues. Thank you.

Mr. BILIRAKIS. And we will break now and show our appreciation to Dr. Woodcock for her patience. I'm sure you understand what we go through here. Thank you.

[Brief recess.]

Mr. BILIRAKIS. The committee is pleased to welcome as our first panelist Dr. Janet Woodcock, who is a Director for the Center for Drug Evaluation and Research with the FDA.

Dr. Woodcock, of course, your written statement is a part of the record. I will set the clock at 10 minutes, please do the best that you can in that regard. We certainly won't cut you off if you should go over. Please proceed.

STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Ms. WOODCOCK. Thank you.

Mr. Chairman and members of the subcommittee, I'm Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration. I'm pleased to be here and be able to provide information on FDA programs that may effect consumer's demand for, and access to pharmaceuticals.

As you're aware, the FDA is not involved in drug pricing. However many of our programs can impact directly or indirectly on health care costs related to drugs. Our generic drug review program is the best example. The availability of lower cost generic versions of innovator drugs has a substantial impact on lower cost to consumers in the healthcare system.

Today I will discuss issues related to three FDA programs: Generic review, the agency's regulation of direct-to-consumer advertising, and the process of switching drugs available under prescription to over-the-counter status.

The generic drug program has the most straight forward impact on drug costs. In fiscal year 2000 alone, FDA approved 232 generic drugs. Some of these were first time approvals, while others represented additional competitive entries into the marketplace. It has been well documented that when generic competition is introduced, drug prices drop. Because FDA review provides assurance that generic products are fully substitutable for the innovator drug, patients can save money on their medicines without fear of getting a lower quality product.

FDA's generic drug review program implements that Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Waxman-Hatch Amendments. These amendments were intended to balance two important public policy goals. First, to provide meaningful market protection incentives to encourage the development of valuable new drugs. And second, to provide for the rapid availability of generic versions once the statutory patent protection and marketing exclusivity of the innovator drug expired.

And overall, as we've already heard, the program has, and is currently achieving these goals. However, as might be expected when so much is at stake financially, certain provisions have proved challenging to implement. In particular, the 180 day generic exclusivity procedure has been marked by litigation, court decisions, and course directions for FDA. These problems are too complex to discuss in my brief statement, but they're fully covered in my written testimony, and I'll be glad to answer any questions you might have.

The bottom line is that the generic drug program is functioning well, but there are difficulties in implementation of certain parts of the statute. And I would like to also add that these difficulties have increased in recent years, and we may project that the trajectory of problems may be increasing.

Now I'd like to turn to the issue of direct-to-consumer advertising. First, I'd like to point out that direct-to-consumer advertising has always been legal in the United States. Neither the Food, Drug and Cosmetic Act nor the implementing regulations, which were first issued in the 1960's, prohibit promotion to consumers or patients.

People often ask us when FDA lifted its ban on direct-to-consumer advertising. In fact, this activity was never banned. Product sponsors back in the 1960's just didn't advertise to consumers. In the early 1980's, however, a few firms started advertising their prescription products directly to patients. As a result of the ensuing concerns, FDA requested in 1983 that sponsors voluntarily suspend these ads to give FDA time to conduct research and hold public meetings, which was done and the industry complied with this request.

In 1985 FDA withdrew the voluntary moratorium stating that the regulations provided sufficient safeguards to protect consumers. After that there was a steady growth of print direct-to-consumer ads for prescription drugs.

By the late 1990's increasing numbers of reminder ads began to appear on television. These ads can mention the name of the drug, but don't mention its use, which is very confusing to the public, although not to health professionals who are familiar with drug names.

In 1997, in response to the changed information environment in the country, as well as the confusing broadcast situation and the demand from patients and consumers for understandable prescription drug information, FDA issued a draft guidance explaining how sponsors could meet the regulatory requirements for consumer access to complete label information. Sponsors followed this guidance and used it to run broadcast ads.

In 1999 FDA issued the guidance in final form and stated our intention to assess the impact of the guidance and of DTC promotion in general on the public health, and we will do this.

From the public health perspective direct-to-consumer advertising is a double edged sword. On one side we know that many conditions with preventable, serious consequences are severely undertreated in the U.S. population. Examples include hypertension, high cholesterol and mental illnesses. Many people are suffering, or will die prematurely, because they have not utilized available treatments for these conditions. This is such a severe

problem that some public health advocates have suggested to the FDA that certain medicines for cardiovascular problems be switched to over-the-counter status so more people would have access.

Advertising and promotion can strongly influence behavior, that's why firms pay for it. Ads could reach out to untreated individuals and motivate them to seek care. And, in fact, when we've looked at broadcast ads, a significant number of them target these serious and undertreated disorders.

The sword's other edge, though, is that patients and consumers could be motivated by advertising to seek medication that was not right for them and even to pressure prescribers into inappropriate choices. We certainly have heard stories from some health care professionals of patients coming to the office waving such an ad for an inappropriate drug for them.

Again, I cannot cover all issues raised by DTC advertising in a brief statement. When discussing DTC ads and drug costs it's important to stress that not all drug cost increases are negative from a public health standpoint. If more citizens take drugs to prevent heart attacks, strokes, or weakened bones as a result of direct-to-consumer advertising, that is for the public good. If cost increases reflect inappropriate prescriptions or preferential prescribing of more expensive choices, then that's a poor bargain indeed for the public.

Finally, I'd like to say a word about switching drugs from prescription to over-the-counter status. Usually when such switches are considered, the benefits that we think of at FDA involve consumer access and convenience. We do not think about drug costs. In the vast majority of cases historically the drug manufacturer proposes and supports such a switch.

Recently FDA was petitioned by a health care payer group to switch certain prescription antihistamines to over-the-counter status. While FDA does not consider costs in making OTC switch decisions, it is likely that both the petitioner's desire for the switch and the manufacturer's reluctance about the switch is at least in part related to economic factors.

In summary, FDA operates a number of programs that impact people's access to, and knowledge about, available drug treatment. We strive to do this in a way that produces the maximum public health benefit within the current statutory framework that's available to us.

Thank you.

[The prepared statement of Janet Woodcock follows:]

PREPARED STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency). I am here today to update you on three important areas that CDER is continuing to work on:

(1) FDA's implementation of provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) that govern the generic drug approval process.

(2) The promotion that manufacturers of prescription drugs (product sponsors) direct toward consumers and patients. This is referred to as "direct-to-consumer" promotion or DTC.
(3) The mechanism for reclassification of drugs from prescription to over-the-counter (OTC) status, namely, the request for the OTC switch by a third party, a novel situation FDA is presently facing.

I. GENERIC DRUGS

FDA's implementation of provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) govern the generic drug approval process. These provisions give 180 days of marketing exclusivity to certain generic drug applicants. The 180-day generic drug exclusivity provision is one component of the complex patent listing and certification process, which also provides for a 30-month stay on generic drug approvals while certain patent infringement issues are litigated.

The Hatch-Waxman Amendments are intended to balance two important public policy goals. First, drug manufacturers need meaningful market protection incentives to encourage the development of valuable new drugs. Second, once the statutory patent protection and marketing exclusivity for these new drugs has expired, the public benefits from the rapid availability of lower priced generic versions of the innovator drug.

Statutory Provisions

The Hatch-Waxman Amendments amended the Federal Food, Drug, and Cosmetic (FD&C) Act and created section 505(j). Section 505(j) established the abbreviated new drug application (ANDA) approval process, which permits generic versions of previously approved innovator drugs to be approved without submission of a full new drug application (NDA). An ANDA refers to a previously approved NDA (the "listed drug") and relies upon the Agency's finding of safety and effectiveness for that drug product.

The timing of an ANDA approval depends in part on patent protections for the innovator drug. Innovator drug applicants must include in an NDA information about patents for the drug product that is the subject of the NDA. FDA publishes patent information on approved drug products in the Agency's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) (described in more detail below). The FD&C Act requires that an ANDA contain a certification for each patent listed in the Orange Book for the innovator drug. This certification must state one of the following:

(I) that the required patent information relating to such patent has not been filed;
(II) that such patent has expired;
(III) that the patent will expire on a particular date; or
(IV) that such patent is invalid or will not be infringed by the drug, for which approval is being sought.

A certification under paragraph I or II permits the ANDA to be approved immediately, if it is otherwise eligible. A certification under paragraph III indicates that the ANDA may be approved on the patent expiration date.

A paragraph IV certification begins a process, in which the question of whether the listed patent is valid or will be infringed by the proposed generic product may be answered by the courts prior to the expiration of the patent. The ANDA applicant who files a paragraph IV certification to a listed patent must notify the patent owner and the NDA holder for the listed drug that it has filed an ANDA containing a patent challenge. The notice must include a detailed statement of the factual and legal basis for the ANDA applicant's opinion that the patent is not valid or will not be infringed. The submission of an ANDA for a drug product claimed in a patent is an infringing act if the generic product is intended to be marketed before expiration of the patent, and therefore, the ANDA applicant who submits an application containing a paragraph IV certification may be sued for patent infringement. If the NDA sponsor or patent owner files a patent infringement suit against the ANDA applicant within 45 days of the receipt of notice, FDA may not give final approval to the ANDA for at least 30 months from the date of the notice. This 30-month stay will apply unless the court reaches a decision earlier in the patent infringement case or otherwise orders a longer or shorter period for the stay.

The statute provides an incentive of 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification and running the risk of having to defend a patent infringement suit. The statute provides that the first applicant to file a substantially complete ANDA containing a paragraph IV certification to a listed patent will be eligible for a 180-day

period of exclusivity beginning either from the date it begins commercial marketing of the generic drug product, or from the date of a court decision finding the patent invalid, unenforceable or not infringed, whichever is first. These two events—first commercial marketing and a court decision favorable to the generic—are often called "triggering" events, because under the statute they can trigger the beginning of the 180-day exclusivity period.

In some circumstances, an applicant who obtains 180-day exclusivity may be the sole marketer of a generic competitor to the innovator product for 180 days. But 180-day exclusivity can begin to run—with a court decision—even before an applicant has received approval for its ANDA. In that case, some, or all, of the 180-day period could expire without the ANDA applicant marketing its generic drug. Conversely, if there is no court decision and the first applicant does not begin commercial marketing of the generic drug, there may be prolonged or indefinite delays in the beginning of the first applicant's 180-day exclusivity period. Approval of an ANDA has no effect on exclusivity, except if the sponsor begins to market the approved generic drug. Until an eligible ANDA applicant's 180-day exclusivity period has expired, FDA cannot approve subsequently submitted ANDAs for the same drug, even if the later ANDAs are otherwise ready for approval and the sponsors are willing to immediately begin marketing. Therefore, an ANDA applicant who is eligible for exclusivity is often in the position to delay all generic competition for the innovator product.

Only an application containing a paragraph IV certification may be eligible for exclusivity. If an applicant changes from a paragraph IV certification to a paragraph III certification, for example upon losing its patent infringement litigation, the ANDA will no longer be eligible for exclusivity.

Court Decisions and FDA Actions

This 180-day exclusivity provision has been the subject of considerable litigation and administrative review in recent years, as the courts, industry, and FDA have sought to interpret it in a way that is consistent both with the statutory text and with the legislative goals underlying the Hatch-Waxman Amendments. A series of Federal court decisions beginning with the 1998 Mova[1] case describe acceptable interpretations of the 180-day exclusivity provision, identify potential problems in implementing the statute, and establish certain principles to be used by the Agency in interpreting the statute.

In light of the court decisions finding certain FDA regulations inconsistent with the statute, the Agency proposed new regulations in August 1999 to implement the 180-day exclusivity. Since then many comments have been submitted and there have been additional court decisions further interpreting the 180-day exclusivity provision and complicating the regulatory landscape. The Agency has not yet published a final rule on 180-day exclusivity. As described in a June 1998 guidance for industry, until new regulations are in place, FDA is addressing on a case-by-case basis those 180-day exclusivity issues not addressed by the existing regulations.

One of the most fundamental changes to the 180-day exclusivity program that has resulted from the legal challenges to FDA's regulations is the determination by the courts of the meaning of the phrase "court decision." The courts have determined that the "court decision" that can begin the running of the 180-day exclusivity period may be the decision of the district court, if it finds that the patent at issue is invalid, unenforceable, or will not be infringed by the generic drug product. FDA had interpreted the "court decision" that could begin the running of 180-day exclusivity (and the approval of the ANDA) as the final decision of a court from which no appeal can be or has been taken—generally a decision of the Federal Circuit. FDA's interpretation had meant that an ANDA applicant could wait until the appeals court had finally resolved the patent infringement or validity question before beginning the marketing of the generic drug. FDA had taken this position so that the generic manufacturer would not have to run the risk of being subject to potential treble damages for marketing the drug, if the appeals court ruled in favor of the patent holder. The current interpretation means that if the 180-day exclusivity is triggered by a decision favorable to the ANDA applicant in the district court, the ANDA sponsor who wishes to market during that exclusivity period now may run the risk of treble damages if the district court decision is reversed on appeal to the Federal Circuit. As a practical matter, it means that many generic applicants may choose not to market the generic and thus the 180-day exclusivity period could run during the pendency of an appeal.

In one of the cases rejecting FDA's interpretation of the "court decision" language in the statute, the court determined that the applicant who relied in good faith on

[1] *Mova Pharmaceutical Corp. v. Shalala,* 140 F.3d 1060, 1065 (D.C. Cir. 1998).

FDA's interpretation of the 180-day exclusivity provision should not be punished by losing its exclusivity. The court, therefore, refused to order FDA to begin the running of 180-day exclusivity upon the decision of the district court in the patent litigation at issue. FDA has taken a similar approach in implementing the courts' decisions: the new "court decision" definition will apply only for those drugs for which the first ANDA was submitted subsequent to March 30, 2000. In adopting this course, a primary concern for the Agency was to identify an approach that would minimize further disruption and provide regulated industry with reasonable guidance for making future business decisions.

To advise the public and industry of this position, FDA published a Guidance for Industry in March 2000. FDA intends to incorporate the courts' interpretation of the "court decision" trigger for 180-day exclusivity into the final rule implementing the changes in 180day exclusivity.

Orange Book Listings

There have been concerns expressed over FDA's role in the listing of patents in the Orange Book, which can have an impact on generic drug approvals by delaying approval and 180-day exclusivity. Under the FD&C Act, pharmaceutical companies seeking to market innovator drugs must submit, as part of an NDA or supplement, information on any patent that 1) claims the pending or approved drug or a method of using the approved drug, and 2) for which a claim of patent infringement could reasonably be asserted against an unauthorized party. Patents that may be submitted are drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method of use patents. Process (or manufacturing) patents may not be submitted to FDA.

When an NDA applicant submits a patent covering the formulation, composition, or method of using an approved drug, the applicant must also submit a signed declaration stating that the patent covers the formulation, composition, or use of the approved product. The required text of the declaration is described in FDA's regulations. FDA publishes patent information on approved drug products in the Orange Book.

The process of patent certification, notice to the NDA holder and patent owner, a 45-day waiting period, possible patent infringement litigation and the statutory 30-month stay mean there is the possibility of a considerable delay in the approval of ANDAs as a result of new patent listings. Therefore, these listings are often closely scrutinized by ANDA applicants. FDA regulations provide that, in the event of a dispute as to the accuracy or relevance of patent information submitted to and subsequently listed by FDA, an ANDA applicant must provide written notification of the grounds for dispute to the Agency. FDA then requests the NDA holder to confirm the correctness of the patent information and listing. Unless the patent information is withdrawn or amended by the NDA holder, FDA will not change the patent information listed in the Orange Book. If a patent is listed in the Orange Book, an applicant seeking approval for an ANDA must submit a certification to the patent. Even an applicant whose ANDA is pending when additional patents are submitted by the sponsor must certify to the new patents, unless the additional patents are submitted by the patent holder more than 30 days after issuance by the U.S. Patent and Trademark Office.

FDA does not undertake an independent review of the patents submitted by the NDA sponsor. FDA does not assess whether a submitted patent claims an approved drug and whether a claim of patent infringement could reasonably be made against an unauthorized use of the patented drug. FDA has implemented the statutory patent listing provisions by informing interested parties what patent information is to be submitted, who must submit the information, and when and where to submit the information. As the Agency has stated, since the implementation of the 1984 Hatch-Waxman Amendments began, FDA has no expertise or resources with which to resolve complex questions of patent coverage, and thus the Agency's role in the patent-listing process is ministerial. The statute requires FDA to publish patent information upon approval of the NDA. The Agency relies on the NDA holder or patent owner's signed declaration stating that the patent covers an approved drug product's formulation, composition or use. Generic and innovator firms may resolve any disputes concerning patents in private litigation. As noted above, if the generic applicant files a paragraph IV certification and is sued for patent infringement within 45 days, there is an automatic stay of 30 months, substantially delaying the approval of the generic drug and, thus, the availability of lower cost generic drug products.

CONCLUSION

FDA continues to implement the Hatch-Waxman Amendments exclusivity provisions in the best manner possible given the text of the legislation, the history of the legislation and the numerous court challenges. Again, as previously noted, FDA has tried to balance innovation in drug development and expediting the approval of lower-cost generic drugs.

II. DIRECT TO CONSUMER ADVERTISING

Statutory and Regulatory Authority

The promotion that manufacturers of prescription drugs (product sponsors) direct toward consumers and patients is referred to as "direct-to-consumer" promotion or DTC. Such promotion uses multiple avenues for reaching lay audiences, including, but not limited to: television and radio advertisements, print advertisements, telephone advertisements, direct mail, videotapes and brochures. It is important to understand the scope of FDA's authority in this area. It is also important to understand the different types of advertisements that are directed toward consumer audiences.

The FD&C Act and regulations do not distinguish between professional and consumer audiences. Section 502(n) of the FD&C Act specifies that prescription drug advertisements must contain "a true statement of . . . information in brief summary relating to side effects, contraindications, and effectiveness" of the advertised product. The implementing regulations (Title 21, *Code of Federal Regulations* [CFR] Section 202.1), originally issued in the 1960s, specify, among other things, that prescription drug advertisements cannot be false or misleading, cannot omit material facts, and must present a fair balance between effectiveness and risk information. Further, for print advertisements, the regulations specify that every risk addressed in the product's approved labeling must also be disclosed in the advertisements.

For broadcast advertisements, however, the regulations require ads to disclose the most significant risks that appear in the labeling. The regulations further require that the advertisement either contain a summary of "all necessary information related to side effects and contraindications" or convenient access must be provided to the product's FDA- approved labeling and the risk information it contains.

Finally, the FD&C Act specifically prohibits FDA from requiring prior approval of prescription drug advertisements, except under extraordinary circumstances. Also, the advertising provisions of the FD&C Act do not address the issue of drug product cost.

Types of Advertisements

There are three different types of ads that product sponsors use to communicate with consumers: "product-claim" advertisements, "help-seeking" advertisements, and "reminder" advertisements. Advertisements that include both a product's name and its use, or that make any claims or representations about a prescription drug, are known as "product-claim" advertisements. These ads must include a "fair balance" of risks and benefits. In addition, they must provide all risk information included in the product's FDA-approved labeling or, for broadcast advertisements, provide convenient access to this information. In our regulations, the phrase "adequate provision" is used to identify the convenient access option. Unlike the "product claim" ads, "help-seeking" advertisements and "reminder" ads need not include any risk information.

A "help-seeking" advertisement discusses a disease or condition and advises the audience to "see your doctor" for possible treatments. Because no drug product is mentioned or implied, this type of ad is not considered to be a drug ad and FDA does not regulate it.

The second type of advertisement that does not need to include risk information is called a "reminder" advertisement. The regulations specifically exempt this type of ad from the risk disclosure requirements. Like "help-seeking" ads, the "reminder" ad is limited, although in a different way from "help-seeking" ads. "Reminder" ads are allowed to disclose the name of the product and certain specific descriptive (e.g., dosage form) or cost information, but they are not allowed to give the product's indication or dosage recommendations, or to make any claims or representations about the product. The exemption for "reminder" ads was included in FDA's regulations for promotions directed toward health care professionals, who presumably knew both the name of a product and its use. "Reminder" ads serve to remind health care professionals of a product's availability. They specifically are not allowed for products with serious warnings (called "black box" warnings) in their labeling.

Evolution of DTC Promotion

Prior to the early 1980s, prescription products were not promoted directly to consumers and patients. Instead, product sponsors often produced materials that were given to health care professionals to pass on to patients if they thought this would be appropriate for particular patients. In the early 1980s, a few companies started advertising products directly to patient audiences (specifically, older people concerned about pneumonia and people taking prescription ibuprofen to treat arthritis pain). As a result of questions and concerns about promotion directed toward non-health care professionals, in 1983 FDA requested that sponsors suspend DTC ads to give the Agency time to study the issue.

The industry complied with this request, and during the ensuing moratorium FDA conducted research and sponsored a series of public meetings. In 1984, the University of Illinois and Stanford Research Institute jointly sponsored a symposium to discuss consumer-directed prescription drug advertising from a broad research and policy perspective. On September 9, 1985, FDA withdrew the moratorium in a Federal Register (FR) Notice (50 FR 36677), which stated that the "current regulations governing prescription drug advertising provide sufficient safeguards to protect consumers."

During the early 1990's, product sponsors increasingly used consumer magazines to advertise their products. These ads typically included a promotional message together with the "brief summary" of adverse effects, similar to that used in physician directed ads. The "brief summary" statement, which frequently appears in small print, is not very consumer friendly. In the 1990s, product sponsors also started using television advertisements in a limited fashion. Television advertisements were limited because FDA and industry did not believe that it was feasible to disseminate the product's approved labeling in connection with the ad. The extensive disclosure needed to fulfill this requirement essentially precluded the airing of such ads. For example, one way to satisfy this requirement would be to scroll the "brief summary," which would take a minute or more even at a barely readable scrolling rate. The industry, therefore, resorted to television ads that did not require risk disclosure.

By the mid-1990s, product sponsors started placing "reminder" ads on television. Because these ads only mentioned the name of the drug, however, they were extremely confusing to consumers, who, unlike health care professionals, were not knowledgeable about the name and the use for these products.

In response to increasing consumer demand for information, FDA began to consider whether broadcast advertisements could be constructed to ensure access to product labeling, the only alternative to including all of an advertised product's risk information. FDA considered suggestions about providing access to multiple sources of product labeling as a means of satisfying the requirement that consumers have convenient access to FDA-approved labeling when manufacturers broadcast a "product-claim" advertisement.

In August 1997, FDA issued a draft guidance entitled: "Guidance for Industry: Consumer-Directed Broadcast Advertisements" that clarified the Agency's interpretation of the existing regulations. The Guidance described an approach for ensuring that audiences exposed to prescription drug advertisements on television and radio have convenient access to the advertised product's approved labeling. The proposed mechanism consisted of reference in the broadcast advertisement to four sources of labeling information: a toll-free telephone number, a website address, a concurrently running print advertisement, and health care professionals. Following a comment period, and detailed review and consideration of the comments, FDA made only minor changes to the draft guidance, and issued it in final form in August 1999 (64 FR 43197, also found at http://www.fda.gov/cder/guidance/1804fnl.htm). In announcing the final guidance, FDA advised that the Agency intended to evaluate the impact of the guidance, and of DTC promotion in general, on the public health, within two years of finalizing the guidance.

Stakeholder Perspectives

A number of stakeholder groups have expressed strong interest in DTC promotion. Those that are positive about DTC promotion assert that this practice will:

- Improve consumers' knowledge of drugs and drug availability.
- Encourage consumers to talk with their health care providers about their health problems.
- Allow consumers and patients to have a greater role in decisions about their own health care that they say they desire.
- Improve communication between patients and their physicians.
- Improve appropriate prescribing by allowing physicians to get more information about their patients from their patients.

- Lower the cost of prescription drugs. Not all stakeholders are positive about DTC promotion. Opponents assert that DTC advertising will:
  - Confuse consumers about drugs.
  - Make it appear that prescription drugs are safer than they are.
  - Interfere with the patient-physician relationship because patients will insist that their physicians prescribe the advertised products.
  - Increase inappropriate prescribing.
  - Raise the cost of prescription drugs.

Finally, there is a group of stakeholders with a less polarized view of DTC promotion. They believe that such promotion has both benefits and risks, but that it should be strictly regulated, and that, preferably, all DTC materials should be "pre-approved" by FDA. They often assert that there are potential public health benefits associated with patients visiting health care providers about untreated diseases or conditions, particularly those that appear to be under treated in the population and that are responsible for long-term harm (for example, high cholesterol, high blood pressure, diabetes and osteoporosis).

Current Situation

FDA recognizes that drug promotion raises certain issues for health care professionals and different issues for consumers, in light of differences in medical and pharmaceutical expertise. For this reason, FDA has monitored DTC promotion, and especially broadcast promotion, very closely to help ensure that adequate contextual and risk information, presented in understandable language, is included to fulfill the requirement for fair balance and to help the consumer accurately assess promotional claims and presentations.

Product sponsors of prescription advertisements are required to submit their promotional materials to FDA around the time these materials are initially put into public use. FDA receives approximately 32,000 of these submissions per year, for all types of promotion, including promotion to health care professionals. Product Sponsors also can submit draft materials to FDA for review and comment prior to using them. Division of Drug Marketing, Advertising and Communications (DDMAC) has made it a high priority to provide comments to product sponsors on voluntarily submitted draft broadcast advertisements within a reasonable time. In fact, although it is not required, a majority of product sponsors voluntarily submit their broadcast advertisements to DDMAC for prior review and comment at some point as advertising materials are being produced. Product sponsors may ask for review and comment at the very initial stages of production (by supplying the words they intend to use along with rough drawings of their proposed graphics), or at the later stages of final videotape production. DDMAC only gives final comments on final videotapes because inappropriate presentations can turn an otherwise acceptable advertisement into an unacceptable one (for example, by pacing the risk disclosure too rapidly, including multiple distracting visual images during the risk disclosure, or including images that overstate the efficacy of the product beyond what is supported by substantial clinical evidence).

Since January 1997, sponsors of about 65 prescription drugs have aired "product-claim" advertisements on television or radio. A small number of prescription biological products also have been advertised. Nine products fall into the allergy category (nasal and ocular anti-histamines, and nasally administered corticosteroids), while another eight products treat skin or hair-related problems (acne, cold sores, rosacea, baldness, unwanted facial hair, nail fungus). More importantly, ten products are designed to treat diseases that are believed to be under treated, including high cholesterol and heart disease, and mental health problems like depression. Five products to treat or prevent osteoporosis or menopausal symptoms have been advertised. Other advertised products are approved to treat such conditions or diseases as asthma, Alzheimer's Disease, arthritis, chronic obstructive pulmonary disease, diabetes, insomnia, migraine, obesity, overactive bladder, serious heartburn, smoking cessation, and sexually transmitted diseases. Most of these are serious problems where patients are in the best position to recognize symptoms.

It is important to note that DDMAC does not know how many different advertisements have aired in broadcast media for these 65 drugs. There have been multiple campaigns for a number of the products, including the allergy and high cholesterol products. In addition, many campaigns include different length "product-claim" commercials, as well as multiple short "reminder" commercials. DDMAC does not track the number of different broadcast advertisements that are submitted. Further, because "help-seeking" advertisements, if done properly, are not considered to be drug ads, most product sponsors do not send them to DDMAC under the submission requirements for prescription drug promotional materials. Therefore, we have no measure of how many of these have been in the public domain.

Enforcement Related to DTC Promotion

Since August 1997, FDA has issued:

- 26 "untitled" (or "Notice of Violation") letters on "product-claim" broadcast advertisements. Such letters request that the violative promotion be stopped immediately. Product sponsors virtually always comply immediately with this request.
- 3 "warning letters" on broadcast advertisements. This is a higher-level enforcement action, and requests that a remedial campaign be conducted by the company to correct the impressions left by the ad.
- 13 "untitled" letters on purported "reminder" broadcast advertisements.
- 3 "untitled" letters on purported "help-seeking" broadcast advertisements.

Most of the violations cited were because the ad overstated or guaranteed the product's efficacy, expanded the indication or the patient population approved for treatment, or minimized the risks of the product, through either inadequate presentation or omission of information.

Since January 1997, the Agency has issued:

- 43 "untitled" letters that addressed DTC print advertisements or other promotional materials, including purported "reminder" and "help-seeking" materials.
- 1 "warning letter" that included a DTC print advertisement as part of an overall misleading campaign.

Generally, the violations involving print ads making "product-claim" ads were similar to those cited above. Nearly all "reminder" ad violations were the result of representations about the product that triggered the need for full disclosure of benefits and risks. "Help-seeking" ad violations were due to a particular product being implied in the message. As noted above, however, FDA cannot determine how many specific advertisements serve as the denominator for assessing how many have resulted in enforcement action compared with those that have not.

Research on DTC Promotion

A number of groups have been conducting research on DTC promotion. Much publicly available research consists of surveys utilizing samples of consumers or patients to examine attitudes about DTC promotion and self-reported behaviors related to DTC promotion in the context of patient-physician visits and use of prescription drugs. The groups sponsoring this research include: Prevention magazine, TIME Inc., the National Consumers League, and American Association of Retirement People. A few surveys of physicians have been made partially publicly available. FDA remains concerned, however, about the representation of the physician surveys. In 1999, FDA sponsored a telephone survey that focused on a national probability sample of patients who had seen a physician for a problem on their own within the three months prior to the survey. The results of this patient survey suggested that patients are seeking additional information as a result of DTC promotions that they have seen. This information was sought primarily from health care professionals, and secondarily from reference texts and family. Generally, between 10 and 20 percent of respondents said that they sought additional information from the sources referenced in broadcast advertisements—toll-free telephone numbers, web sites, print advertisements. A major result, and one that is consistent with results of Prevention's national surveys, is that a significant minority of respondents said that a DTC ad has caused them to ask a doctor about a medical condition or illness they had not previously discussed. This could represent a significant and positive public health benefit, particularly if these patients are talking about undiagnosed heart disease or other serious disorders.

The survey results also suggest that DTC advertisements are not significantly increasing visits to a physician's office. For the most part, patients said that they had recently visited their doctors for the traditional reasons: because it was time for a check-up (53 percent), because they were feeling ill (42 percent), or because they had had a sudden symptom or illness (41 percent). Only two percent said that they had visited their doctor because of something they had seen or heard. Of those patients who had a conversation with their doctor about a prescription drug: 81 percent said that their doctor had welcomed the question, 79 percent said that their doctor discussed the drug with them, and 71 percent said that their doctor had reacted as though the conversation was an ordinary part of the visit. Only four percent said that their doctor seemed upset or angry when the patient asked about a prescription drug. According to the patients, therefore, physicians seem to be reacting well to questions about prescription drugs. Finally, only 50 percent of these patients said that their doctor gave them the medication discussed. Thirty-two percent said that the doctor recommended a different drug. Twenty-nine percent of the respondents

indicated that behavioral or lifestyle changes were suggested by the doctor. It therefore appears, from FDA's data, that physicians are comfortable denying prescriptions when the prescription would not be right for the patient.

A small number of patients who were denied prescriptions said that their doctors told them why. Reasons included: the drug wasn't right for the patient; the doctor wanted the patient to take a different drug; the drug had side effects of which the patient was unaware; the patient did not have the condition treated by the drug; the patient did not need a prescription drug; the patient could use a non-prescription drug; and, there was a less expensive drug available.

Patients also were asked about their attitudes about prescription drug advertisements. Their answers indicated somewhat mixed feelings. Eighty-six percent agreed that these ads help make them aware of new drugs, 70 percent agreed that the ads give enough information to help the patient decide if they should discuss the product with a doctor, and 62 percent agreed that ads help the patients have better discussions with their doctors about their health. Only 24 percent agreed that DTC ads make it seem like a doctor is not needed to decide whether a drug is right for someone. In contrast, 58 percent agreed that DTC ads make drugs seem better than they really are, 59 percent agreed that ads do not give enough information about the advertised product's risks and negative effects, and 49 percent agreed that these ads do not give enough information about the benefits and positive effects of the advertised product.

Next Steps

In issuing both the draft and the final broadcast advertisement guidance, FDA stated its intent to assess the impact of the guidance, and of DTC promotion in general, on the public health. FDA is also aware that privately funded research is being planned to examine the effects of DTC promotion. At present, FDA is not aware of any evidence that the risks of DTC promotion outweigh its benefits. FDA intends to carefully examine all available data, to determine whether the public health is adequately protected.

III. PRESCRIPTION DRUG SWITCH TO OVER-THE-COUNTER STATUS

The FDA is responsible for the reclassification of many drugs from prescription to OTC status. These are often referred to as "switch drugs," and the reclassification process is referred to as "switching from prescription to OTC." Nearly forty ingredients incorporated into drug products have been reclassified since 1972 when the OTC drug review began.

Under the FDA's Office of OTC Drug Evaluation, a process was established for producing a final regulation to set standards for each drug product-treatment category. Nearly forty ingredients has been reclassified using this process since 1972 using this process.

Switches are covered by the prescription exemption procedures, found in 21 CFR 310.200. Switches can be initiated by FDA, the sponsor of a new drug application, or by any interested party. The OTC drug product can be marketed under a NDA or under the process established by regulation. The switch may be:

1. A complete switch whereby all of the indications and dosage forms are switched from prescription to OTC status;
2. A partial switch whereby some of the prescription indications and dose regimens are switched to OTC status and the others remain prescription.

Historically, the majority of drugs that have been switched from prescription-only to OTC marketing were at the initiated by the sponsor. The FD&C Act restricts drugs to prescription only status if a learned intermediary is required for the proper use of the drug. As written, the default assumption of the Act is for drugs to be marketed OTC without a prescription unless a decision is made that consumers are not able to appropriately diagnose their condition nor able to correctly choose the remedy and safely use it based on OTC labeling.

Anyone may submit a citizen petition. Individuals sometimes submit petitions, but most come from the regulated industry or consumer groups. For the first time, a third party has asked the FDA to reclassify a drug through the citizen petition process. Because the petition is still under review, we cannot comment on it at this time. FDA may use a wide range of public procedures (e.g., conferences, meetings, correspondence, hearings) during the process of evaluating the petition and to assist in the formulation of a final response.

In the process of responding to a petition, the Agency creates an administrative record, a comprehensive documentary foundation for the agency's final decision. The Agency's grant or denial of a petition, which usually is in the form of a letter to the petitioner, constitutes a final agency action. The Agency may also issue a ten-

tative response explaining that the Agency has not yet reached a final decision on whether to grant or deny the petition. When FDA issues a final decision, however, it may be appealed through the court system.

As with any petition, FDA is studying the scientific and legal issues it raises in an effort to make the best science-based decision under the law.

We look forward to the Committee's continued interest in this area and would be happy to answer any questions.

Mr. BILIRAKIS. Thank you, Dr. Woodcock.

I'll start the questioning and depending on how the day goes and calls for votes, we might go into a second round of questioning of Dr. Woodcock. I've already discussed this with Mr. Brown.

In this first round at least, Dr. Woodcock you used the term, if I heard you correctly, directly substitutable referring to the approval of generics. Do you believe that the public recognizes the fact—well, maybe I should ask you. Do you believe that generics are bio-equivalent directly substitutable to innovator drugs when they've been approved by the FDA?

Ms. WOODCOCK. Yes. We have scientific basis for our decisions on bio-equivalence and substitutability. And we would not approve a generic drug that was not fully substitutable for the innovator drugs.

Mr. BILIRAKIS. Do you believe that the public recognizes the fact that they are in fact directly substitutable and use the term bio-equivalent to those drugs?

Ms. WOODCOCK. I know that members of the public, the pharmacy community and the medical community, some of them have serious doubts about substitutability perhaps for certain drug classes or perhaps overall. There's a lot of misunderstanding about the program.

Mr. BILIRAKIS. We've heard physicians on both sides of the aisles. We had Dr. Coburn who served on this panel who used to make comments, at least to me personally, that he didn't think that all the drugs that were approved as being bio-equivalent actually fell into that category.

What does it mean when we say the drug is bio-equivalent to another drug?

Ms. WOODCOCK. What we mean is that the active ingredient in the drug is available in the same concentration in the pill or injection, or whatever it might be, it's exactly the same as the innovator product and that we know that the rate and extent of absorption into the body of that active ingredient is equivalent. That's what we mean by bio-equivalence; that when you take that pill, for example, you get the same drug level within the body as you would by taking the innovator product.

Mr. BILIRAKIS. Is there any room for error? Is there a safety factor in there somewhere?

Ms. WOODCOCK. All of these measurements have variability to them, particularly bio-equivalence. If you took a drug and I took a drug, it would be very likely we would wind up with slightly different blood levels for a variety of reasons. We have to take that into account when we test generic drugs for bioavailability. But a recent survey that was done showed that innovator products and generic products on absorption into the body, looking at the actual data there was less than 3 percent difference in the tests.

Now, if you tested an innovator product from day-to-day or lot-to-lot, you may well see the same amount of variability, and that's what people don't understand.

Mr. BILIRAKIS. If a patient were on a drug therapy using an innovator drug, could they in the middle of the stream, so to speak, switch into a generic drug that is considered to be bio-equivalent and no problems develop from that essentially?

Ms. WOODCOCK. That is correct.

Mr. BILIRAKIS. That is correct?

Ms. WOODCOCK. And there's no need for additional tests or titration or changes of the dose if they switch to an equivalent generic product.

Mr. BILIRAKIS. In my opening statements, Doctor, thank you for that statement, there's a concern out there I think among many members of the public and still among the medical profession, as we both already said, that they are not bio-equivalent.

Ms. WOODCOCK. That's right.

Mr. BILIRAKIS. I think that's one of the things that I wanted to do in this hearing. I know the subject matter is varied in this hearing, but I wanted to be sure that we were able to project to the American people a feeling of confidence.

In my opening statement I made the comment that FDA seems to take longer to approve generic drugs. Is that true?

Ms. WOODCOCK. The mean time for generic drug approval right now is about 18 months, whereas for a new drug it's around 12 months. That's correct.

Mr. BILIRAKIS. Is there a reason why it takes longer?

Ms. WOODCOCK. Well, significant resources were placed into the new drug review process. FDA added over a 1,000 scientists and reviewers as a result of the Prescription Drug User Fee Act and subsequent changes to that.

Mr. BILIRAKIS. Should it be 18 months versus 12 months? Why? Is there a greater emphasis on safety there, just the fact that we are saying that this non-innovator drug is bio-equivalent and thereof it takes us longer to do it?

Ms. WOODCOCK. The reason the generic drug takes longer, usually, is that the application goes through several cycles. We are responsible for reviewing a generic drug within 180 days and getting an answer back. We only do that right now—we do that about 55 percent of time. We get them reviewed within 180 days. But that's much shorter than 18 months.

The problem is the answer is frequently no, that the generic drug applicant does not meet all the standards and there are remaining questions. Therefore, it must go back to the sponsor. The application must be resubmitted and then another review cycle occurs, and sometimes even a third review cycle occurs that's causing the actual time to getting on the market to be up to 18 months.

Mr. BILIRAKIS. Thank you.

I think we're having problems with the clock. But my time, I believe, has expired.

Mr. Brown to inquire?

Mr. BROWN. Thank you, Mr. Chairman.

I'm not sure I understood that. I understand that it's 12 months—typically an NDA is 12 months and ANDA amended for

the generic is 18 months. Part of the reason for that is Congress passing—I understand part of the reason is Congress passing PDUFA 2 or whatever we ended up calling it under the New Prescription Drug User Fee Act. There are no generic user fees, correct?

Ms. WOODCOCK. That's correct.

Mr. BROWN. But explain why beyond resources, and understanding resources are a big part of it, why is the generic company not able when submitting its application to, in a sense, do it right the first time? Is that a product of inadequate resources in the agency?

Ms. WOODCOCK. I believe there are several factors, and that if the agency were able to provide more assistance to generic firms, then we would have better applications and we would have lower cycles. That's actually what happened under the Prescription Drug User Fee Act. Much of the resources that we have under the User Fee Act go to providing advice and explaining the standards to the sponsors so that the applications are of good quality when they are first submitted.

So, of course, there are other factors that are involved. Some generic firms are smaller, they may be inexperienced, it may be the first time they put a product forward and they have to go through many cycles.

Mr. BROWN. If you assume that name brands have—the name brand approval process, the NDA approval process is adequately resourced, funded, staffed, whatever from the FDA's vantage point and if you would make that same assumption for ANDA if we could in fact fund it however it might be done at an equally adequately, what would the time be—the 18 months would be able to be knocked down to what time period?

Ms. WOODCOCK. It's probably unlikely that we could get to 6 months or something like that.

Mr. BROWN. But certainly less than 12, correct?

Ms. WOODCOCK. Probably that's correct.

Mr. BROWN. I mean it shouldn't—let me interrupt. Sorry.

It should be easier—we should be able to accomplish it more quickly the ANDA than the NDA, right?

Ms. WOODCOCK. I was just going to say that. Exactly, it is a simpler application.

One of the issues is to what extent can we get the generic drug sponsors to submit an approvable application on the first cycle so that it could be reviewed and approved on the first cycle. If that doesn't happen, then the clock will run twice, at least, and it's going to be 1 year.

Mr. BROWN. It seems, Mr. Chairman, that one of the goals of this subcommittee and this full committee should be to bring that period down, that should be something we can agree on across the board in both parties. If it takes 12 months for the new application, that we can't get it to 12 or fewer months for the ANDA. And I know we've talked about it, and your interest is that for sure, too, that it's something we ought to be able to do.

Ms. WOODCOCK. Could I say one more thing about this? There are several factors that are related.

Many of the drug manufacturers for generic drugs are located overseas, particularly the bulk drug applications. And to try and—bulk drug manufacturers. To get to those overseas firms in a timely manner is a challenge, because they're all over the world.

Also, right now we have queues, waiting time, within the Office of Generic Drugs before picking up an application. They have to wait in a queue until the ones in front. We have very strict timeframes. So that's another factor that impacts on our ability to get these out quickly.

Mr. STUPAK. We'll run this point on the drugs. The generic drugs when they do an application do they pay a fee under the User Fee Act?

Ms. WOODCOCK. No.

Mr. STUPAK. But a regular drug, a new drug applications pays about $309,000 I think is the average for a fee?

Ms. WOODCOCK. That's correct.

Mr. STUPAK. So what you're really saying, the process is really driven by whose paying the fee at the time of the application?

Ms. WOODCOCK. The process is driven by the statutory structure that's set up. The fees for prescription drugs—the prescription drug user fees are only allowed to be used for the process of review of new human drugs.

Mr. STUPAK. Well, what you're telling this committee is if you're a generic when you make your application, your chance of being approved in 180 days is 55 percent. But now the new drug companies when they put down a $309,000 fee, the last 2 years you've approved all those within a 100 percent of the time isn't that correct?

Ms. WOODCOCK. This is a continual source of confusion. The review time, time to answer for a generic would be 180 days. It might often be no. That's——

Mr. STUPAK. What's the time to answer on a regular drug, a new drug application?

Ms. WOODCOCK. Twelve months.

Mr. STUPAK. Twelve months.

Ms. WOODCOCK. Yes.

Mr. STUPAK. But you do those 100——

Ms. WOODCOCK. Ten to 12 months.

Mr. STUPAK. [continuing] percent of the time for the last 2 years, right?

Ms. WOODCOCK. We make those deadlines, right. We don't approve them all in that time, but we get an answer back 100 percent of the time, that is correct.

Mr. STUPAK. Thank the gentleman for yielding.

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. Deal to inquire.

Mr. DEAL. Thank you, Mr. Chairman.

And thank you, Dr. Woodcock, for being here today.

I'd like to explore with you briefly the issue of switching a drug from a prescription drug status to an over-the-counter status. And in order to understand that, let me first of all ask you are there some drug applications that FDA approves that are initially nonprescription and over-the-counter? And if so, what percentage would you estimate that might be of applications?

Ms. WOODCOCK. The answer is yes, there are some drugs that are approved directly for the first time as an over-the-counter drug under a new drug application. And it's a very small percentage, perhaps 1 percent. I can't—I don't have the data.

Mr. DEAL. Are those usually at the request of the manufacturer that they be over-the-counter or is that a decision that FDA makes initially in those cases?

Ms. WOODCOCK. We might discuss it. Frequently it is the aim of the manufacturer from the start, but we have discussed it with some manufacturers as to whether—what market their product is most appropriate for.

Mr. DEAL. So in 99 percent of the cases or roughly thereabouts they are asking for a protected prescription type status?

Ms. WOODCOCK. That's correct.

Mr. DEAL. And is the determination in most cases to switch it from prescription to over-the-counter status made during the timeframe of their initial patent protection exclusivity period or is it normally made after that exclusivity has expired?

Ms. WOODCOCK. It's normally made afterward, and there are several factors that go into that.

Mr. DEAL. But normally they have had their initial protected period in which they are allowed to be by prescription only in most cases?

Ms. WOODCOCK. Yes, these things are not exactly linked, all right, and they may be linked economically. But the prescription status has to do with safety and effectiveness concerns about the drug, prescription versus nonprescription status. But you're right.

Mr. DEAL. But in that regard your statement was that the determination by FDA to switch it was not based on a cost factor?

Ms. WOODCOCK. That's correct.

Mr. DEAL. So therefore I assume it is based on a determination that it is now safe to be in a nonprescription status. Does that mean then that FDA conducts ongoing investigations and research to make that determination?

Ms. WOODCOCK. No, we usually do not. I think I ought to stress that most drugs never switch to over-the-counter. The vast majority of drugs remain prescription, and this has to do with what we call OTC-ness, if you'll excuse the term. And that has to do with, can the consumer diagnose this condition themselves, all right, No. 1. And then No. 2, is the drug safe enough to be used in the consumer's hands as far as side effects and so forth.

So we go through a series of factors. Most drugs never switch off prescription status, either because the doctor is needed to diagnose the condition or monitor the condition or because the drug has safety or other issues around it that would not permit it to be used by a consumer. But in cases where there is a possibility for a switch, typically the manufacturer will pursue the additional studies required to demonstrate that OTC-ness.

Mr. DEAL. But I gathered from your initial testimony that in most cases the switches are without the consent and sometimes over the objection of the manufacturer. If that is the case and FDA does not conduct ongoing research to make the determination about whether or not the individual is able to prescribe his own medication, in effect, then how is that determination made? If the manu-

facturer is in effect saying they don't think it is ready to be over-the-counter, but you're saying that it is but you've conducted no research, how do you arrive at that conclusion?

Ms. WOODCOCK. I'm afraid I was unclear. The vast majority of manufacturers want to switch their products, but in this current situation that we're facing, in fact, FDA had to do—had to assume some of the burden of evaluating the safety of these products in response to citizen petition, and also the petitioner submitted data to us as well.

Mr. DEAL. One final question, Mr. Chairman.

Does FDA take the position that it has the authority to switch from prescription to over-the-counter status without the request being made by the manufacturer?

Ms. WOODCOCK. Yes, we have that authority.

Mr. DEAL. And what is the basis, in your opinion, of that authority, which statute?

Ms. WOODCOCK. The Food, Drug and Cosmetic Act, Durham-Humphrey Amendments. We feel there is a presumption of non-prescription marketing of drugs unless there is a need for the learned intermediary to be interposed for safety or effectiveness reasons.

Mr. DEAL. Would that be the authority of Section 503(d)(3)? That's all right to ask, I was given that number myself.

Ms. WOODCOCK. We can get back to you.

Mr. DEAL. All right.

Ms. WOODCOCK. Sorry.

Mr. DEAL. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Pallone to inquire.

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Woodcock, in your testimony you went through some detail about this Orange Book Listing, and I have to say it's a little confusing to me. But it's my understanding that with the patent listing process that the FDA is required to list all patents in this Orange Book and you're not in the business of determining the validity of the patents coming out of the Patent Office, you state that, you just list the submitted patents. And then further on you said if the generic applicant files a paragraph IV certification and is sued for patent infringement within 45 days, there's an automatic stay of 30 months substantially delaying the approval of the generic drug and the availability of lower cost generic drug products.

Now, I guess what I wanted to ask is that it seems like this is an open invitation to submit frivolous patents, you know, just to trigger the 30 month hold on approval for a generic. And in our—Mr. Brown's bill in the GAAP Bill we eliminate this automatic 30 day delay, you know, when the brand name sues a generic. And, you know, I think that is a good thing because, you know, the public has a lot to gain from eliminating these frivolous suits. And, as you say, trying to bring the generics on the market so we can low cost affordable drugs.

I just wanted you—if you would comment on that? I mean, would you be in favor of this provision in the bill, in the GAAP Bill?

Ms. WOODCOCK. The Administration has not finalized its position on that, so I really can't comment.

I will say that, as I indicated in my oral testimony, that in recent years we have seen an increase in paragraph IV certifications and all the ramifications around that, it's been a fairly remarkable increase. And this may reflect the impact of court cases in the last decade and those decisions. And I am concerned about the implications of this for our continuing to operate the generic drug review program.

Mr. PALLONE. Do you have any kind of analysis of that that we could have that you could send us?

Ms. WOODCOCK. We can provide that, yes.

Mr. PALLONE. All right. I'd certainly appreciate it.

Ms. WOODCOCK. We'd be glad to do that.

Mr. PALLONE. But the problem is, it's not so much the law doesn't allow you to look at this, but you just don't have the resources, is that what you're saying?

Ms. WOODCOCK. The statute, if I understand correctly, says FDA shall list—is that correct? Shall publish patent submitted by the innovator——

Mr. PALLONE. So you don't think you legally have the right to look into it?

Ms. WOODCOCK. No, I'm not a lawyer, but that is what our legal interpretation——

Mr. PALLONE. It's more resources, the law's not clear.

Ms. WOODCOCK. Well, I can't interpret the law. I'm sorry.

But if we were asked to do such a thing, I would have to say it would significantly divert resources from the scientific review of generic drugs that we are currently undertaking.

Mr. PALLONE. Okay. Well, I appreciate it if you could send us some information of what you've seen develop in that regard. That would be helpful, I think.

I also wanted to ask you a question about generic biologics. Senator Hatch in a recent speech pointed out that unless a way is found for the FDA to approve generic biologics with the same efficiency that it currently approves other generic drug products, neither the government nor I guess the private sector would be able to afford to pay for the drugs of the future. Do you agree with that? Does the FDA have the authority to approve generic biologics?

Ms. WOODCOCK. Products that are approved under the Public Health Service Act are often considered biologics. It depends on what you mean by biologics. But that statute does not have the provision for generics. So, there's actually no statutory framework.

There are also major scientific issues that relate to the approval of recombinant protein products.

Mr. PALLONE. So, again, it's partially you think that the statute impartially, you know, resources or ability to do it?

Ms. WOODCOCK. That's correct. There are some recombinant products that are approved as drugs and regulated by the Center for Drugs under Section—under the Food, Drug and Cosmetic Act and we are certainly evaluating what path we could follow, because those are subject to Waxman-Hatch Act.

Mr. PALLONE. Okay. Thank you.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Bryant to inquire.

Mr. BRYANT. Thank you, Mr. Chairman.

And let me add my welcome to Dr. Woodcock.

Also, in just following up, I have a couple of quick questions about the advertising issue and understanding that your testimony I think reenforces to some extent an appropriateness of advertising insofar as it reaches under treated conditions and diseases. Could you elaborate on that just a little bit more? Very quickly. I know you referenced it earlier.

Ms. WOODCOCK. Certainly. We looked at, for example, the top causes of death, the diseases that are top causes of death in the United States now, and we looked at the direct-to-consumer advertising that is currently occurring, and many of the conditions leading to death, premature death in the United States are subject to direct-to-consumer ads that have been aired in the last few years.

Now, we recognize that the ads being driven by commercial considerations may not advertise all drugs that are available, only the ones probably that are on patent, for example. But they may have the potential to increase awareness among consumers and patients of these conditions and the availability of effective treatments.

Mr. BRYANT. And ultimately a down side, of course, is that the patient goes to the doctor's office and demands this drug whether it's necessary or not? Of course, the ultimate in that case, too, as the gatekeeper in this situation the doctor has clearly, you know, a duty to say you don't need that drug, you don't have that condition or whatever. So that should work itself out in most every case, I would hope, if the doctor's a competent physician he certainly wouldn't prescribe a drug for a patient that he believed did not need it?

Ms. WOODCOCK. One would hope so. I think we have done some surveys of patients, and that's detailed in my written testimony, and from the patient's point of view this advertising has provided an opportunity for them to go and talk to their doctor and mention their condition and ask is the drug right for me. In many of those cases their physician has said the drug is not right for you, and there have been a variety of reasons; you don't have the condition, this drug is too expensive you should use another drug, or these are side effects you may not wish to face.

Mr. BRYANT. Good. On the over-the-counter issue I understand your testimony that the bulk of FDA's decisions to move it over from a prescribed status over to OTC status, by far and away the majority of these decisions are with the manufacturer's agreement and consent. And, in fact, I assume these are all initiated by the manufacturer. But now——

Mr. BILIRAKIS. Is that right, are they all initiated——

Ms. WOODCOCK. Generally, a vast majority. That's correct.

Mr. BRYANT. Who else would initiate it if not the manufacturer?

Ms. WOODCOCK. Well, sometimes the FDA in past cases have said "Look, this drug looks a lot more like an over-the-counter drug than a prescription drug, maybe you ought to reassess your target or your market."

Mr. BRYANT. Based on what types of studies to show that it was safe to do so?

Ms. WOODCOCK. Right, and based on the——

Mr. BRYANT. Well, who would make the those studies when the FDA initiates it?

Ms. WOODCOCK. The sponsor has agreed with that and gone ahead and targeted the product toward the OTC world.

Mr. BRYANT. Do you have other entities or groups that have initiated these types of requests before?

Ms. WOODCOCK. Not historically, but we can't foresee what the future may hold. It may become more common.

Mr. BRYANT. Can you give me any example of where there's been another party, particularly a third party payer or an insurance company that's done this before?

Ms. WOODCOCK. We tried to search our memory banks for this, and we could not come up with an example where this exact scenario has occurred before.

Mr. BRYANT. The reason I asked this is that I take one of the drugs that's in play here, and I was back in my District over the weekend and I had a constituent come up to me unsolicited not knowing we were going to have this hearing and ask about this, and they take that same drug. And they're not really happy, as I'm not really happy about this being perhaps transferred over to an OTC category simply based on economic reasons. And I know an awful lot of the physicians out there that originally were in this business also are concerned with this. And I would hope that the FDA would take all this into consideration.

I think we're breaking new ground here, if I'm not wrong, and perhaps setting some bad precedent and perhaps too much interference in allowing economic driven reasons to have too much of a play in terms of medical treatment.

So, again, I would hope that if indeed—and I stress the word if the FDA has that authority to make this switch even over the objection of the manufacturer, I would hope the FDA would look down the road also and say "Well, whose going to do the safety testing" if you've got a manufacturer who opposes this transfer and, again, to look at those types of considerations, too.

Do you have an opinion? This would be my last question in this round. You know, over the objection of manufacturer, who would perform the safety tests that are necessary before the FDA would—to allow the FDA in effect to make this switch in categories?

Ms. WOODCOCK. These are very product line specific. In the case of the antihistamines, as you know, all sorts of allergy medicines and antihistamines are over-the-counter already. In addition, there's been a marketing history of these products in question. That would be quite different for some other product at some other stage of its marketing, for example.

So I can't give a specific question, but obviously we need the safety data base, FDA, to make these kind of evaluations. And I can assure you that economics will not play a role in our decision-making. I understand, and we all understand there are economic factors on both sides of this particular issue. And that's not the basis for FDA's evaluation of these issues.

Mr. BILIRAKIS. Should the FDA have that authority, the unilateral authority that you insist they have? Should they have it?

Ms. WOODCOCK. To switch a product over-the-counter? Yes, we——

Mr. BILIRAKIS. You think you should have or you shouldn't have that authority?

Ms. WOODCOCK. Yes, I think that is appropriate. We think that's appropriate. We have that authority now.

Mr. BILIRAKIS. And you think it's appropriate.

Mr. BRYANT. Mr. Chairman, again, could I just follow up, and I'm not sure I had the answer on who will do the safety testing under those——

Mr. BILIRAKIS. We're going to have a second round, Ed.

Mr. BRYANT. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Stupak?

Mr. STUPAK. Thank you, Mr. Chairman.

Doctor, in the direct-to-consumer advertising in your testimony you said in August 1999 that you did a final regulation on it and then you go on to say that in announcing the final guidance, the FDA advised the agency intended to evaluate the impact of the guidance and of direct-to-consumer promotion in general on the public health within 2 years of finalizing the guidance.

Ms. WOODCOCK. Yes.

Mr. STUPAK. So it'll be August of this year? Two years from 1999?

Ms. WOODCOCK. Yes.

Mr. STUPAK. So are you going to wait until August of 2001 or have you been reviewing the impact?

Ms. WOODCOCK. We have been reviewing the impact. We have some addition—as I said, we've done consumer survey, which of course doesn't totally evaluate public health impact. It gives one side of the picture. We're trying to work with private parties in academia and do further surveys.

Mr. STUPAK. So in response to I think it was Mr. Bryant's question, you said something about deaths related to—you were concerned about that. Explain that again to me.

Ms. WOODCOCK. Death?

Mr. STUPAK. Yes, I thought you said deaths, maybe I misheard you.

Ms. WOODCOCK. No. I'm sorry. I don't know what part of——

Mr. STUPAK. All right. Okay. So thus far in your 2 year review that's been going on how is direct-to-consumer advertising working? You mentioned about patients coming in saying I want this. Has it increased the risks of improper drugs being supplied and have all the risk with direct-to-consumer advertising then been given to the consumer before they go into that doctor waving this advertisement to them?

Ms. WOODCOCK. Right. As I said, we have done a consumer survey. We have—the Consumer's Report about their encounters with physicians, and that is detailed in my testimony. And what they have said is that this has spurred their conversations with their doctors, but in not all cases have they received the drug that they went to ask about or the condition.

Mr. STUPAK. You know, consumers tell us that they spend less time with their doctors. Are you saying direct-to-consumer advertising actually have patients spending more time with their doctors discussing?

Ms. WOODCOCK. Well, what we hope that one of the benefits is that it will focus on the discussion between the physician and the patient on what is appropriate therapy, if any, for that condition.

Mr. STUPAK. And the final decision for the therapy, though, is left to the physician, correct?

Ms. WOODCOCK. Always for prescription drugs.

Mr. STUPAK. Let's get back to the application fee submitted by new drug applications and generic drugs. In PDUFA, it was, wasn't it? Prescription Drug User Fee Act, when that came about did it distinguish that the money as generated from these new applications would only be used for new drug applications or did it distinguish that—did it say that generics could not be used?

Ms. WOODCOCK. Yes. It restricted the use of the funds to new drug applications or the process of review of new human drugs. We also use it for IND investigational drug review.

Mr. STUPAK. But would it exclude generics?

Ms. WOODCOCK. Yes. We have to keep very careful books and we cannot expend any funds from user fees on generic review.

Mr. STUPAK. Well, if the generics put forth the user fee, would that get them processed quicker?

Ms. WOODCOCK. Well, I guess that would be up to the Congress.

Mr. STUPAK. Well, you tell me that, you know, you have 180 days to make a decision on generic.

Ms. WOODCOCK. That's correct.

Mr. STUPAK. But on a new drug, it's 1 year?

Ms. WOODCOCK. Yes.

Mr. STUPAK. And generics have to go through two or three cycles, but it seems like new drug applications only have to go through one cycle, which is a 12 months deal and they get approved.

Ms. WOODCOCK. Many of them. By no means all of them.

Mr. STUPAK. But in the last 2 years according to the L.A. Times article they would have been approved 100 percent. So for the last 2 years those new drug applications been a 100 percent approval within the cycle?

Ms. WOODCOCK. No. People mix up approval and making our review times. We've 100 percent met our review times, many of those are a turn down.

Mr. STUPAK. Okay. What about review time with generic drugs, do you meet all of those?

Ms. WOODCOCK. No, only 55 percent.

Mr. STUPAK. 55 percent?

Ms. WOODCOCK. Right now.

Mr. STUPAK. So if you meet a 100 percent review time but only 55 with generics, would that number improve if there was money attached to the application?

Ms. WOODCOCK. I think we could always do more with more.

Mr. STUPAK. Sure. So it really comes down to whether or not you're dedicating the resources to generic drugs is really the issue?

Ms. WOODCOCK. It's certainly one of the factors that goes into the current approval times, which are 18 months.

Mr. STUPAK. Okay. So it's really not poor application by generic drug applications, it's just you don't have the resources available at the FDA to process them in a timely manner?

Ms. WOODCOCK. Well, for example, in the Prescription Drug User Fee program back in the 1990's when this was started, one of the factors that was identified in the 3 year time to approval was that a poor quality of applications.

Mr. STUPAK. Okay.

Ms. WOODCOCK. And part of that program was to work to develop very clear standards and guidance and assistance in meeting the standards.

Mr. STUPAK. Okay.

Ms. WOODCOCK. And having high quality applications. That is something that could—we could ramp up our effort in the generic drug program.

Mr. STUPAK. You haven't done that with the generics saying here's how you improve your applications, the standards and here's what you've got to meet?

Ms. WOODCOCK. We've done it within—we've done a lot within our limits of our ability and we have brought the times down.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Burr to inquire.

Mr. BURR. Thank you, Mr. Chairman.

Welcome, Dr. Woodcock.

Ms. WOODCOCK. Thank you.

Mr. BURR. It's been a while. We're glad to have you back.

Ms. WOODCOCK. Thank you.

Mr. BURR. Let me ask you a few questions, if I could. I've tried to do catch up and reading your testimony that the FDA fully feels they have the authority to make a switch. Let me ask you about the process of that. Is that a written procedure of what the FDA goes through when petitioned either by a company for a switch to over-the-counter status, an outside group or in this most recent case, a third party?

Ms. WOODCOCK. Yes. The OTC office established procedures that we go through.

Mr. BURR. And how much interaction would they have with the line folks who actually go through the new drug applications on prescription drugs? How much are they involved in the process?

Ms. WOODCOCK. They're very deeply involved in the process.

Mr. BURR. Well, we would hope that they are.

If the FDA can make a switch over the objection of a drug manufacturer, which I think we conclude you believe you can, can it do so without disclosing information which is otherwise protected by the Food, Drug Act and the Trade Secrets Act?

Ms. WOODCOCK. I don't think so. I'd like to ask our lawyers. I have Kim Dettelbach here. Would you like to comment on that? You'll have to come up to the table. Or would you prefer not to comment?

Mr. BURR. Would one interrupt that all the information is available post approval or is there information that is protected?

Ms. WOODCOCK. I think the answer, perhaps, to your question is that we obviously can't disclose trade secret information and that is an issue that we would have to deal with.

Mr. BURR. And is there a written process as to how you deal with that?

Ms. WOODCOCK. As I said in my testimony, we really haven't faced this particular set of issues previously.

Mr. BURR. If a manufacturer objects to a forced switch to over-the-counter status and refuses to remove the Rx from its label, the prescription from its label, what recourse would the FDA have and

would this be misbranding in violation of Food, Drug and Cosmetic Act?

Ms. WOODCOCK. I'd prefer not to answer that question right now, because it's a legal question. But I believe we would have legal recourse that we could take.

Mr. BURR. Okay. That's sufficient.

Ms. WOODCOCK. All right.

Mr. BURR. Upon the submission of a new drug application can the FDA force a drug to be sold over-the-counter though the manufacturer may wish to sell the drug by prescription only? In other words, can you make the determination of an over-the-counter direction at the beginning of the application based upon your authority today?

Ms. WOODCOCK. Yes, I believe that would be the same as our authority to force a switch. It would be much less likely because of the lack of data available on that particular drug at the beginning of the process.

Mr. BURR. So it is unlikely that the FDA would use their authority to make that determination at the beginning of the filing process of an application?

Ms. WOODCOCK. Only if adequate data were available to satisfy all the criteria for OTC-ness.

Mr. BURR. Are there any other classification of drugs that you can think of that would be considered today for over-the-counter status?

Ms. WOODCOCK. The FDA had a meeting, a public meeting in June of this year, last year. I'm sorry. Of last year to discuss the whole OTC program, and at that time a wide variety of medicines, classes of medicines were brought up and discussed as far as being candidates for OTC switching. In the vast majority of cases, in all the other cases I think except the one we're talking about here today, the antihistamines, the manufacturers were supportive of such switches.

Mr. BURR. So there's no other classification that the FDA can perceive today where one would consider it a forced switch where a manufacturer was not in agreement?

Ms. WOODCOCK. Not to my knowledge.

Mr. BURR. Okay. One last question if I could. How much money is spent today on direct-to-consumer advertising by pharmaceutical companies?

Ms. WOODCOCK. I think $2.5 billion.

Mr. BURR. $2.5 billion. Is the FDA fairly confident of that number, because I think Members of Congress have heard—per year, yes.

Ms. WOODCOCK. Per year.

Mr. BURR. But I think the trade journals have had it as high as $11 billion at some point, and I'd love to have an accurate number of direct-to-consumer advertising?

Ms. WOODCOCK. Yes. Well, we're not an economic agency. We don't go out and directly survey these things. We rely on commercially published information. The information that we have is that the vast majority of pharmaceutical advertising is still directed toward the physicians or other prescribers, and that's about $13-14 billion a year total advertising, of which——

Mr. BILIRAKIS. Does the FDA keep track of dollars that are spent for that type of advertising?

Ms. WOODCOCK. That's not required to be submitted to us. We do not have jurisdiction over that, over those type of economics.

Mr. BILIRAKIS. So where did we get this? That's from the broadcasters?

Ms. WOODCOCK. This is from published information on firms that commercially keep track of these matters. And we can provide you our sources.

Mr. BURR. Dr. Woodcock, I'm told that $2.5 billion is inclusive of samples and other marketing efforts, not—11 is inclusive?

Ms. WOODCOCK. Yes.

Mr. BURR. $2.5 is broadcast?

Ms. WOODCOCK. That's correct.

Mr. BURR. Okay.

Ms. WOODCOCK. No, not broadcast. Direct-to-consumer.

Mr. BURR. Direct-to-consumer advertising.

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. BURR. I thank Dr. Woodcock. I hope she won't be a stranger to this committee.

And, Mr. Chairman, let me say that I'm disappointed that I wasn't here for Mr. Brown's opening statement. He told me it was elegant, and I believe every word of it.

Mr. BILIRAKIS. It was directed to the gentlemen.

Mr. Green to inquire.

Mr. GREEN. Thank you, Mr. Chairman.

And to follow up my colleague from North Carolina, I appreciate the chairman calling this hearing today so we can talk about Mr. Brown's legislation.

Dr. Woodcock, I appreciate your being here, and I know the issue is the over-the-counter versus prescription, and I know the FDA's interest is only the consumer safety. It's interesting that for the protagonists in this case, whether they are WellPoint or the pharmaceutical industry, obviously their interest is cost. And our concern overall is the cost to our constituents, whether it's cheaper over-the-counter because they have insurance coverage, or if it's cheaper on prescription.

In knowing that it didn't—the FDA didn't move into this area very quickly. This was actually filed in 1998, so it's taken 3 years. The FDA didn't move very lightly in making this decision.

But also, you did not look at all into the cost factors, it was only in the consumer safety?

Ms. WOODCOCK. Right. We have not made a decision. We have completed an advisory committee that has advised us on safety. And we're still evaluating what we're going to do. But, no, we did not move quickly, very quickly. We had to gather a lot of data, as was already alluded to, and we did not take cost into account.

Mr. GREEN. The committee didn't take cost? Will the FDA take the cost into consideration?

Ms. WOODCOCK. No. We've certainly heard a lot about it on both sides from many parties, but that's not part of our role.

Mr. GREEN. Okay. Let me go on and ask some questions about a lot of our concern on the generics.

Out of the approximately 500 cases where a generic has filed for a paragraph IV certification, how many of these cases were settled out of court, do you know, just a rough percentage? I understand it's about 90 percent. Is that correct?

Ms. WOODCOCK. All right. Well, I don't know. I don't have that data right now. I can provide it to you to the extent we know that.

Mr. GREEN. So 90 percent, use that as an example and that's what I understood that 90 percent. And does the FDA have any jurisdiction over these settlement agreements?

Ms. WOODCOCK. No.

Mr. GREEN. And so the Waxman-Hatch statute requires that settlement agreements contain provisions to ensure that generics market their products immediately, and yet the FDA doesn't have any authority under Waxman-Hatch Act to be able to overlook or oversee those settlement agreements that extend the patent?

Ms. WOODCOCK. Right, that's correct. That's correct.

Mr. GREEN. But the FTC, Federal Trade Commission, has authority or jurisdiction over anti-competitive behavior?

Ms. WOODCOCK. That's correct.

Mr. GREEN. Is there ever any correlation or work between the FDA and the FTC?

Ms. WOODCOCK. Certainly. We talked to them when these issues first arose, in fact.

Mr. GREEN. Okay. And it seems like if the percentages are 500 cases are filed and there's 90 percent settlement, and yet our regulatory agency the FDA is taken out of it, it seems like that would impact the cost to the consumers in generics versus the patent drugs.

If a brand company could file a new patent at the end of the original patent expiration and receive an automatic 30 month stay and then negotiate for additional time because of the 180 day exclusivity this could result really in years of patent extension?

Ms. WOODCOCK. Yes.

Mr. GREEN. And that's a concern I know, and like I said, I haven't really focused on my colleague Mr. Brown's bill until today and this hearing has caused me to do that and realize that, and even Mr. Waxman agrees that we need to fix it.

The other concern we hear from the next panel the talk about the patent stacking. And I understood I think in one of your answers you were interested or the FDA was going to look at the issue of patent stacking?

Ms. WOODCOCK. Yes.

Mr. GREEN. So where a brand company introduces a new patent toward the end of the patent's original expiration date to give it even longer time of market exclusivity. Is there anything in the statute that would prevent these brand companies from doing this now?

Ms. WOODCOCK. Not to my knowledge.

Mr. GREEN. There's no regulatory authority FDA would have?

Ms. WOODCOCK. No.

Mr. GREEN. In fact, again, these companies receive an automatic 30 month stay if their patents are challenged.

Ms. WOODCOCK. That's correct.

Mr. GREEN. So another 2½ years?

Ms. WOODCOCK. That's right.

Mr. GREEN. And again, my colleague who used to sit here, but Peter Deutsch and I, we actually in our opening statements didn't collaborate but both of us were concerned about it, and I don't fault someone who is a lawyer in an earlier life for using the system but, obviously, they're gaming the system to the detriment of our consumers.

So, thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Ehrlich.

Mr. EHRLICH. Doctor, thanks first of all.

Your testimony is very illuminating and it's not only educational for us but it helps us educate our constituents with regard to—in fact, I'm meeting a number of my constituents in an hour. I'm going to relay some of your observations, but particularly over weekends when we go home we get a lot of these questions.

I think your observation with regard to truth in advertising is well taken. It certainly can be consumer friendly with regard to education, but it also obviously drives demand, which is one of the issues we're trying to deal with here.

Just a couple observations with regard to what you said. Clearly an application fee with regard to generics and the additional income that would bring into the agency would shorten the review time. That's your testimony today, is that fair?

Ms. WOODCOCK. Well, as I said, we can do more with more. I think we are performing well in getting generic drugs out, but clearly there are limitations now.

Mr. EHRLICH. With regard to clearly a lot of questions on the OTC process, and that's really the purpose of this hearing today, your testimony in that regard has been educational as well. You've cited individual criteria, and that's one of the most important pieces of your testimony that we're going to take away today as we go back and talk to our constituents are those individual elements that really make up the process. And what I've heard you talk about, you've been very clear that money, cost is irrelevant and you've talked about convenience, clearly.

Ms. WOODCOCK. Yes.

Mr. EHRLICH. And safety, obviously. And this more subjective, I guess, test with regard to self diagnoses. I'd like to hear a little more about that. And then with regard to a number of questions from colleagues, in that you've talked about available data not generated in house, but generated by manufacturers?

Ms. WOODCOCK. Yes.

Mr. EHRLICH. Any other individual criterion that you would cite today with regard to the entire process and then a further—if you can, further objective description with regard to the self-analysis?

Also, a personal note as a sufferer at this time of the year I appreciate what you all have been doing with regard to bringing this stuff out quicker, including antihistamines and the like. So, that's a personal note.

But if you can just give me your comments with regard to the process?

Ms. WOODCOCK. Well, certainly. For all OTC drugs, if I understand your question, you're asking what kind of criteria are there for a drug to be OTC versus prescription, is that right?

Mr. EHRLICH. Correct. Correct. The list?

Ms. WOODCOCK. The list? All right.

One of the major criteria would be that the condition that the patient is able to figure out that they have the condition. And there has been an evolution over the last 20 years on what we as a society feel, think that patients can diagnose and manage. And we've already basically decided that patients can diagnose what we all allergic rhinitis. In other words, hay fever. They can tell when they have hay fever and select choices, because there are many choices out in the OTC market. So that's very important.

For many of the other drugs that there's a lot of debate about right now about OTC switching, there are still significant questions that remain about self-diagnoses, and those are drugs—we're requests for drugs for cholesterol lowering, for example, to go over-the-counter. And the question is can the consumer adequately diagnose the fact they have high cholesterol and that this would be appropriate intervention for them. And that story is still evolving.

So, that's the major criterion. If the consumer cannot appropriately select for themselves, diagnose their condition, then OTC is off the table.

Then for any particular drug to treat that condition would have to have certain characteristics. It would have to have an adequate safety profile. It wouldn't have to need medical monitoring to maintain its safety or its effectiveness.

As you know, when you go to the doctor sometimes they will take tests of your blood or whatever while you're taking a drug or an EKG, or they'll do different things to make sure that drug is still right for you; it's working or it's safe. Those kind of interventions can't be used in the OTC setting.

We also frequently have what's called label comprehension studies. And that sounds complex, but what it means is can you write directions for use for that product that the average consumer who has that condition can read and understand and then will go ahead and use the product appropriately? Because people do all sorts of things, as we all know. Sol that's another piece that we look at. Can a label be written that's comprehensible to a consumer.

So those are the kind of criteria. Effectiveness also would need to be something that the consumer in some way could tell whether the drug was working or not. And traditional OTC drugs have been for symptomatic conditions where you know you have a problem.

Mr. BILIRAKIS. The gentleman's time has expired. And we do have a second record.

Mr. EHRLICH. Thank you for the specificity. I appreciate that.

Ms. WOODCOCK. Certainly.

Mr. BILIRAKIS. Mr. Towns inquire.

Mr. TOWNS. Thank you very much, Mr. Chairman.

Dr. Woodcock, given the explosion in the use of the Internet, even if the FDA modified its guidance on advertising, aren't we still likely to have product promotion occur? Only this time it won't be from the manufacturer, but from users of the Internet?

Ms. WOODCOCK. That's true, and that's been going on for a long time in the print and other media. And the Internet is no different, except that the information can get around a lot faster to a lot more people. But FDA only regulates promotion by sponsors or

manufacturers, distributors, repackers and so forth. We don't regulate statements by other citizens about drug use.

Mr. TOWNS. Well, I think the problem here is how likely is that Internet generated promotional information to be accurate and contain the necessary safety warnings for the consumers? I mean, you have to be concerned about that.

Ms. WOODCOCK. We certainly have been monitoring that, and there's a wide variety of quality of information on the Internet. Some of it is very high quickly and some of it is highly inaccurate, and that is a general safety problem.

Mr. TOWNS. And that's going to get—I mean continue.

Ms. WOODCOCK. Right. Well, that's part of the importance of the prescriber in making sure that when people get prescription drugs that they're appropriate for them.

Mr. TOWNS. Right. I think you might have answered this question before. I think when I came in I thought I heard part of it.

In your experience do generic manufacturers have the expertise to produce the kind of information that the FDA would require to move a prescription to over-the-counter status?

Ms. WOODCOCK. Could you repeat the question?

Mr. TOWNS. Yes. I asked do generic manufacturers have the expertise to produce the kind of information that the FDA would require to move a prescription to over-the-counter status?

Ms. WOODCOCK. Absolutely not. We have generic copies of innovator over-the-counter drugs available.

Mr. TOWNS. In your opinion why have there been so few patent issues raised in regard to the generic applications with the FDA since the inception of the Waxman-Hatch Act in 1984?

Ms. WOODCOCK. I don't know. That would require me to read into the minds of the people who would file these, and I don't know.

Mr. TOWNS. No, in your opinion?

Ms. WOODCOCK. Well, I think there have been quite a few in recent years, and they were fewer in the past and the prominence of different court decisions and the impact of those court decisions has changed the landscape, that's what I believe.

Mr. TOWNS. Well, let me ask this then: In your opinion if there was one element of the Waxman-Hatch Act that should be changed to promote the production of more generics, what would it be?

Ms. WOODCOCK. Well, as I said, the Administration hasn't finalized its evaluation of that and I don't have an opinion at this point.

Mr. TOWNS. All right. Let me try it another way. I'm not going to give up.

If there was one element that should be changed to protect the interests of brand name products, in your opinion what would it be?

Ms. WOODCOCK. The interests of brand name products?

Mr. TOWNS. Yes. Then I'll try it another way. No, go ahead.

Ms. WOODCOCK. Well, it hasn't really been posed to me that way. Much of this hearing has been about protecting the interests of brand name products yet providing for prompt availability of generic products once the patents expire. I think that is the central issue that we're discussing here.

Mr. TOWNS. I agree, but I mean in your opinion—I mean, could you—you wouldn't want to make a comment on it?

Ms. WOODCOCK. Well, I believe that the subjects that have been discussed here today, the 180 day exclusivity, the 30 month stay are central issues that we're going to have to deal with.

Mr. TOWNS. All right. Thank you.

I yield back, Mr. Chairman.

Mr. BILIRAKIS. Are you suggesting that we should take another look at the 180 day exclusivity and the 30 month stay?

Ms. WOODCOCK. Well, I believe FDA has really been struggling with these issues, with the court decisions and the changing landscape. It's been difficult for us.

Mr. BILIRAKIS. Let me ask you on the OTC situation, does FDA have set up any sort of a remedy, if you will, or an appeal process or whatever on the part of—since you feel that you have the unilateral authority to make that decision, do you have any sort of a process for the manufacturer to take or even the public? Because as long as it's prescription, there would, depending on the insurance policy and that sort of thing, there would be coverage to a large degree. But once it goes over-the-counter generally there won't be any coverage.

Ms. WOODCOCK. Well, there's administrative—we have a formal appeals process with the center for appealing decisions. And there's also the administrative process, formal administrative process in hearings and so forth that could be pursued by anyone who disagrees with an FDA decision.

Mr. BILIRAKIS. You haven't experienced that yet insofar as this particular issue is concerned?

Ms. WOODCOCK. No. No, but this is a new issue.

Mr. BILIRAKIS. Yes. And you're expecting to experience it on this issue?

Ms. WOODCOCK. I don't know.

Mr. BILIRAKIS. You don't know? All right.

Just very quickly, Doctor. You're an M.D., have you practiced medicine?

Ms. WOODCOCK. Yes.

Mr. BILIRAKIS. You have? Okay. So as a medical doctor because you're concerned and care about patients, would say without any hesitation that if a generic drug is approved by the FDA, that it is directly substitutable and bio-equivalent to the innovative drug?

Ms. WOODCOCK. That's correct. I use generics when they're available. I use generics for my family. Prescribe generics for patients. I believe there's a lot of ignorance and misunderstanding out there about the generic program.

Mr. BILIRAKIS. Good. Thank you for that.

Mr. Brown, we're in the second round now, and we're going to have to break right after Mr. Brown inquires. We will break until we have the vote, and then unfortunately we'll have to ask you to wait.

Mr. BROWN. Thank you for that very direct answer to the chairman, too, and putting people's mind at rest I think in large part. And the chairman and I have talked about that from time-to-time. Thank you for that.

The PhRMA witness in the next panel wrote that "generic applications have not raised or encountered any patent issues that have delayed their approval." Is that statement essentially correct in your experience?

Ms. WOODCOCK. I've not encountered any patent issues——

Mr. BROWN. I mean generic applications according to the former witness in the next panel, "have not raised or encountered any patent issues that have delayed their approval."

Ms. WOODCOCK. No, they have not. Okay. I'd like to ask Gary Buehler, who is the head of the Office of Generic Drugs to answer that question, if I may.

Mr. BROWN. Mr. Chairman?

Mr. BILIRAKIS. It's all right with me if he'll speak up.

Mr. BUEHLER. We presently have nine active litigation cases going in the Office of Generic Drugs. Five of them involve patents. And each of these cases involves basically a challenge that is holding up generic drug work or could possibly.

Mr. BROWN. And that's another word, phrase for delay their approval, correct?

Mr. BUEHLER. Correct.

Mr. BROWN. Okay.

Mr. BUEHLER. It may not actually right now be delaying the approval, but it could if it continues.

Ms. WOODCOCK. For any of them?

Mr. BUEHLER. Yes.

Ms. WOODCOCK. There are some that are actually delaying approval is your comment.

Mr. BROWN. So I wonder why PhRMA would make that statement? I guess is that a good reason for all of you to stick around and find out in the next panel.

Most of the blockbuster drugs coming off their initial patents in recent years, Prozac and Prilosec and others, have been involved in paragraph IV certifications that challenge in many cases successfully essentially invalid patents designed to perpetuate the monopoly of the innovator firm well after their original patent has expired, right? I mean, it's done through these paragraph IV applications, correct?

Ms. WOODCOCK. Yes.

Mr. BROWN. Okay. Well, Mr. Chairman, one thing I would like to also ask and ask consent if you could to keep the record open for written questions for other panelists?

Mr. BILIRAKIS. Yes. That is routine. By all means that will be the case and I'm sure you don't mind responding to those as soon as you can?

Ms. WOODCOCK. Not a bit.

Mr. BILIRAKIS. We should really break now unless Mr. Pallone wants to limit his inquiry to maybe about a minute or so.

Mr. PALLONE. You don't want her to wait until we come back?

Mr. BILIRAKIS. Well, I'd rather excuse her if we can. But on the other hand, I don't want to cut you off.

Mr. PALLONE. There could be others, too, that want to ask. Why don't we wait.

Mr. BILIRAKIS. All right. I guess we'll have to wait.

Ms. WOODCOCK. That's fine.

Mr. BILIRAKIS. All right. We're going to recess for a few minutes until we cast this vote.

[Brief recess.]

Chairman TAUZIN. The committee will please come back to order. Mr. Bilirakis has had to be excused for a while. I apologize for that.

I understand we're on the second round of questions right now, and the clerk will advise me as to whose up next. Mr. Pallone is recognized for a round of questions.

Mr. PALLONE. I just wanted to yield to Mr. Brown briefly.

Mr. BROWN. Thank you. And, Mr. Chairman, welcome, good to have you here.

Chairman TAUZIN. Good to be here.

Mr. BROWN. I wanted to correct a statement of so that it's not that I do not misconstrue PhRMA's testimony. I'd said that there were no patent delays—PhRMA's actual words was that there are an overwhelming number of cases there are no delays. And I would content, while I apologize for the slight misquoting that I did, I think that they're still as, Dr. Woodcock said, there are several very significant very costly issues involved there where there are delays. And it's not just a significant problem, it's a growing problem. So for the slight misquote, I apologize, but I think the issue is still very much in front of us.

And I thank the gentleman.

Mr. PALLONE. Thank you.

I wanted to ask Dr. Woodcock, following up on your statement you made to Mr. Brown about the bio-equivalency of generics and your use of generics, I have a bill the Generic Drug Access Act that prohibits states from passing laws keeping generic drugs off the market once the FDA has determined that a generic drug is therapeutically equivalent to a brand name product. And I guess I wanted to ask you two things.

First of all, if you can express an opinion on that whether you think that's a good idea, which you probably won't. But second, you know, to what extent you have seen states act in this to go beyond that in ways that you think are really not effective or really don't make sense and if you have any reports or anything on that?

Ms. WOODCOCK. Yes, I can't comment specifically on the bill, proposed bill. But I can say that I think there is a lot of misunderstanding about the generic program. I think sometimes it is promulgated by innovator companies either in a sincere belief that their product is different than the generic product, or through other motives. And that believe is widespread in the community and some of the pharmacy and medical community that some generics are not equivalent to the innovator product. And these misconceptions are really a problem because we've never—we always follow up on reports we get of therapeutic in equivalence. We get many reports; we switched our patient and the drug didn't work. We've never found a problem with these products when we followed up.

Mr. PALLONE. Have you any—I mean I believe strongly that a lot of times these efforts are made in the State legislature by, you know, brand names just to basically create more problems for generics to come to the market. I mean, is there evidence of that or would you comment on that?

Ms. WOODCOCK. Well, we certainly have seen efforts by innovator firms to state that their product is different than the generics and that there are problems with the generics. We certainly have seen that. We feel—we've had to tell firms they can't make these statements because it's kind of comparative claim that they can't make.

We don't feel these warrant. But you recognize human behavior, you get a pill that's a different color or it looks different or something, and then you think well this is different and I'm really worried it's going to have a different effect.

Mr. PALLONE. Okay. Let me ask you a second question. You know, again, I have difficulty following these things. You commented extensively on the 180 day exclusivity period and the court decisions, and your having to come up with new guidelines, I guess some of which are still outstanding. And, you know, it seems to me again going back to our GAAP Bill, under the GAAP Bill the 180 day exclusivity period granted to the first to file generic applicant would become available to the next filed applicant if the first to file generic company reaches a financial settlement with the brand name to stay out of the market or fails to go to market within reasonable period. It seems to me that that's a way of preventing, you know, some of the problems that you've identified with the 180 day market exclusivity, and I just wanted to know if you would comment on that? I mean, it seems that if we could change the law, then when we don't have you constantly having to deal with all these court decisions and coming up with new guidelines. If you'd comment on that?

Ms. WOODCOCK. I can't comment specifically on the bill, however I think whatever legislation is approached would have to be approached very carefully because of the law of unintended consequences.

I'm sure when the Waxman-Hatch Amendments were put into place some of these outcomes were not necessarily foreseen at the time. And now our regiment or statutory and regulatory regiment is extremely complicated and——

Mr. PALLONE. Do you have any other suggestions maybe in lieu of that to deal with the problem, in lieu of what GAAP proposed?

Ms. WOODCOCK. No, I can't comment. I can't make suggestions. Sorry.

Mr. PALLONE. Okay. Thank you.

Thank you, Mr. Chairman.

Chairman TAUZIN. I thank the gentleman.

The Chair is going to going to ask a round of questions.

And, Dr. Woodcock, I want to ask you to give your own opinion on this. I understand you cannot—are not prepared to give FDA's position on this, but I want to ask you with reference to the 180 day generic exclusivity provision of Waxman-Hatch Act, and basically I want to know whether you think it's still necessary?

The fact is that some people, including the original folks who negotiated the bill for the generic industry, Mr. Engleberg and I understand Liz Dickinson of the FDA's general counsel's office speaking for herself have both commented that there's so much of a financial incentive to challenge patents, that challenges will occur irrespective of exclusivity. What's your personal opinion on that?

Ms. WOODCOCK. I'm not qualified, you know, I'm a physician. I'm not really qualified to comment on the financial incentives for companies. I would defer to those trade associations and other people who really——

Chairman TAUZIN. But you're aware of the fact that people are lining up to challenge, isn't that correct?

Ms. WOODCOCK. Yes, that's correct.

Chairman TAUZIN. And isn't that quite evident now in the history of Waxman-Hatch Act that challengers do in fact line up because the financial incentives are so great?

Ms. WOODCOCK. No, they're lining up——

Chairman TAUZIN. I suppose it must be because financial incentives are great.

Ms. WOODCOCK. They're lining up to challenge, but also at this point there's a 180 day exclusivity is provided.

Chairman TAUZIN. Yes, but again only through the first challenge?

Ms. WOODCOCK. Right.

Chairman TAUZIN. So there's still a lot of other people challenging?

Ms. WOODCOCK. Sure.

Chairman TAUZIN. And, you know, the comments of the folks who negotiated this are basically questioning whether you still need the 180 day exclusivity provision if in fact challengers are lining up without the benefit of it. And without asking you again to comment on the financial incentives, you will concede that that is in fact the case that there is a growing list of challenges now, right?

Ms. WOODCOCK. That's correct.

Chairman TAUZIN. Okay. Second, has the FDA perceived any recent trends wherein manufacturers of larger selling drugs are listing patents in the Orange Book shortly before the previous patents are set to expire?

Ms. WOODCOCK. Yes, we feel that we have observed this trend.

Chairman TAUZIN. It's a clear trend, is it not?

Ms. WOODCOCK. That we believe, yes.

Chairman TAUZIN. If so, does that concern you at all?

Ms. WOODCOCK. As I said earlier, we are concerned with the recent court cases, with the other problems that we're encountering in implementing this provision it's going to become even more complicated and difficult to promptly approve generic drugs.

Chairman TAUZIN. Okay. And finally, does the FDA believe that the rolling exclusivity provision contained within the Brown-Emerson legislation would be an impedient to generic competition in that the exclusivity would continue to bounce from the first to the second to the third challenger if the previous challenge is lost in court?

Ms. WOODCOCK. I'm sorry, but again I'm not able to comment on that. I feel, based on my experience in trying to administer some of——

Chairman TAUZIN. We understand there was testimony on the Senate side indicating that on a personal level again, that the FDA representative there believed that that was of great concern. You're not ready to share that concern?

Ms. WOODCOCK. Not as—no. No. What I was going to say, though, is that with many of these provisions simplicity is a virtue.

Chairman TAUZIN. All right. Thank you very much.

Mr. Greenwood is next, right. Mr. Deal in the Chair.

Mr. Greenwood is recognized for 5 minutes.

You want to Chair?

Mr. DEAL. No, no, you go ahead. Play musical chairs.

Mr. Greenwood.

Mr. GREENWOOD. Mr. Chairman, I'm going to pass for the moment. I just arrived and I need to get a little organized. So, if Mr. Brown——

Mr. BROWN. I don't have any second round questions.

Mr. GREENWOOD. Well then neither do I. I'll just pass and wait for the next ones.

Mr. DEAL. Dr. Woodcock, we want to thank you very much for being here today. We apologize for the fact for the fact that some of us had to come in and out, the votes and other things conflicted, but we do appreciate your appearance today. And I do recall that there were several issues that you indicated you would get back to us in writing, and we would appreciate a follow up response.

Ms. WOODCOCK. That's correct. I will do that. And thank you.

Mr. DEAL. Thank you.

We'll call the second panel today, would they please to come to the table.

Lady and gentlemen, we wish to thank you for appearing here today, and I'll introduce the panel very briefly.

First of all, Dr. Gregory Glover who is partner with a Washington firm and is appearing on behalf of the Pharmaceutical Research and Manufacturers of America.

Mr. Bruce Downey, who is the Chairman and CEO of Barr Laboratories and also, I understand, is appearing on behalf of the Generic Pharmaceutical Association.

And Dr. Jane Delgado, who is President and CEO of the National Alliance for Hispanic Health.

And Mr. John Golenski, who is the Executive Director of RxHealthValue here in Washington.

Mr. Thomas Geiser, who is General Counsel for WellPoint Health Networks. And I believe Dr. Seidman is accompany you as well and Vice President of Pharmacy.

And Mr. Richard Kingham, who is a partner in Covington & Burling here in Washington.

Lady and gentlemen, we appreciate your patience in waiting for your appearance here on this panel.

And, Dr. Glover, we will begin with you.

STATEMENTS OF GREGORY J. GLOVER, ROPES & GRAY ON BEHALF OF PHARMACEUTICAL RESEARCHERS AND MANUFACTURERS OF AMERICA; BRUCE L. DOWNEY, CHAIRMAN AND CEO, BARR LABORATORIES, ON BEHALF OF THE GENERIC PHARMACEUTICAL ASSOCIATION; JANE L. DELGADO, PRESIDENT AND CEO, NATIONAL ALLIANCE FOR HISPANIC HEALTH; JOHN D. GOLENSKI, EXECUTIVE DIRECTOR, RX HEALTH VALUE; THOMAS GEISER, GENERAL COUNSEL, WELLPOINT HEALTH NETWORKS ACCOMPANIED BY ROBERT SEIDMAN, VICE PRESIDENT, PHARMACY; AND RICHARD F. KINGHAM, COVINGTON AND BURLING

Mr. GLOVER. Thank you. Mr. Chairman and members of the subcommittee, on behalf of the Pharmaceutical Research and Manufacturers of America I thank you for inviting me here today to testify on the Waxman-Hatch Act. I am a licensed physician and a practicing attorney with the law firm of Ropes & Gray, and I specialize in intellectual property law and FDA regulatory issues.

PhRMA companies are the source of virtually all new drugs in the United States and the evidence confirms that our innovation in our industry benefits consumers. The research based pharmaceutical industries investment in R&D has jumped more than $30 billion this year. During the last decade the industry has developed more than 370 new life saving cost effective medicines and the pace of innovation is increasing. Our industry now has more than 1,000 medicines in development.

We strongly believe the U.S. pharmaceutical market is robust, competitive and working to the benefit of consumers and patients. It is working, in fact, as Congress intended when it passed the Waxman-Hatch Act.

We believe that advocates of change have a burden to show that change is necessary and would not upset the balance between innovation and generic competition achieved by Congress. But advocates for change have not met that burden. Today almost all innovative medicines face generic competition after their patents expire. The generic industry's share of the prescription drug market is almost 50 percent today compared to less than 20 percent in 1984. And today generic copies often come to market as soon as the patent in an innovative produce expires, whereas before in 1984 it took 3 to 5 years for a generic drug to enter the market.

Contrary to the assertions of the generic industry, this system is working well. Of the more than 8,000 generic applications that have been filed since 1984, fewer than 500 have raised any patent issues, meaning 94 percent have raised no patent issues whatsoever.

Despite the success of the Waxman-Hatch Act generic manufacturers are advocating major change in the legislation that would jeopardize future innovation. I would like to respond specifically to four of the issues that have been raised.

The first issue is patent dispute settlements between pioneers and generics. The actions of the Federal Trade Commission in challenging some recent settlements demonstrate that the anti-trust authorities are actively and adequately monitoring settlements between partner companies and generic manufacturers. Accordingly,

there is no need to amend the Waxman-Hatch Act to deal with this issue.

The second issue is Orange Book Listings. FDA's Orange Book serves two purposes. First, it provides notice to a generic applicant of the patents that cover a pioneer product, and second it provides a mechanism by which innovator companies can initiate litigation of patent disputes prior to FDA approval of a potentially infringing product.

The generic industry proposes to restrict the ability of pioneers to litigate patent disputes prior to FDA approval by limiting the types of patents that can be listed. Restricting Orange Book Listings will hurt both the pioneer and the generic companies. It is in the interest of both parties to have complete and full listings of patents.

The third issue is the 30 month stay of approval. The generic industry contends that it is unfair for FDA to be barred from approving a generic application for up to 30 months while the pioneer attempts to resolve any patent disputes. The generics cannot have it both ways. If it were not for the Waxman-Hatch compromise, an innovator could sue an infringing generic manufacturer when it begins product development. The generic industry cannot reasonably claim the right to engage in development activity that normally would be considered patent infringement and at the same time assert there should no opportunity to resolve these patent disputes prior to product approval. The research based industry should not be condemned for defending patents that are presumed to be valid under U.S. law.

The fourth issue is the so called late listed patents. The purpose of the preapproval litigation procedure is to protect innovator companies from the injury that would occur if generic manufacturers sell infringing products and are unable to pay the potentially large amounts that would be due at the conclusion of the litigation. This rationale applies to all patents regardless of when the patent is issued. Innovator companies should not be deprived of one of the most important rights conferred by the Waxman-Hatch Act simply because a patent is issued by the Patent and Trademark Office after NDA approval and is timely listed in the Orange Book.

None of the proposed changes have merit, none can be made without jeopardizing future innovation and, accordingly, none of these changes should be considered in isolation from the needs of those patients awaiting cures.

I'll be pleased to answer any questions that members of the committee may have.

Thank you.

[The prepared statement of Gregory J. Glover follows:]

PREPARED STATEMENT OF GREGORY J. GLOVER, FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Mr. Chairman and Members of the Subcommittee: On behalf of the Pharmaceutical Research and Manufacturers of America, I am pleased to appear at this hearing today on the Hatch-Waxman Act, direct-to-consumer advertising of prescription drugs, and the switching of drugs from prescription to over-the-counter status. I am a physician and an attorney with the law firm of Ropes & Gray, specializing in intellectual-property and FDA regulatory issues. PhRMA represents the country's major research-based pharmaceutical and biotechnology companies, which are lead-

ing the way in the search for new cures and treatments that will enable patients to live longer, healthier, and more productive lives.

HATCH-WAXMAN

Turning first to Hatch-Waxman, PhRMA strongly believes that the U.S. pharmaceutical market is robust, competitive, and working to the benefit of consumers and patients—is working, in fact, as Congress intended when it passed the delicately-balanced Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act after its principal sponsors). We believe that advocates of change have a heavy burden to clearly show that change is needed and would not upset the careful balance achieved by Congress, as discussed immediately below. They have not met that burden.

Generics Flourish

On the one hand, the generic industry has flourished since the passage of the 1984 compromise law eliminated the barriers to entry and made it much easier, far less costly, and quicker for low-cost generic drug manufacturers to get their copies of innovator medicines to market following patent expiration.

- Since 1984, the generic industry's share of the prescription-drug market has jumped from less than 20 percent to almost 50 percent.
- Before 1984, it took three to five years for a generic copy to enter the market after the expiration of an innovator's patent. Today, generic copies often come to market as soon as the patent on an innovator product expires. And in most cases, sales of pioneer medicines drop as much as 75 percent within weeks after a generic copy enters the market.
- Prior to 1984, only 35 percent of top-selling innovator medicines had generic competition after their patents expired. Today, almost all innovator medicines face such competition.

Research Incentives Preserved

On the other hand, the research-based pharmaceutical industry—the source of virtually all new drugs in the U.S.—was provided limited incentives for innovation under the 1984 law, which restores part of the patent life lost by pioneer medicines as a result of regulatory review by the Food and Drug Administration (FDA). The industry, spurred by accelerating scientific and technological advances, continues to increase its investment in R&D and to develop new, more advanced, and more effective medicines.

- The industry's investment in pharmaceutical R&D has jumped from $3.6 billion in 1984 to more than $30 billion this year.
- During the 1990s, the industry developed 370 new life-saving, cost-effective medicines—up from 239 in the previous decade.
- The research-based pharmaceutical industry now has more than 1,000 new medicines in development—either in human clinical trials or at FDA awaiting approval. These include more than 400 for cancer; more than 200 to meet the special needs of children; more than 100 each for heart disease and stroke, AIDS, and mental illness; 26 for Alzheimer's disease; 25 for diabetes; 19 for arthritis; 16 for Parkinson's disease, and 14 for osteoporosis.

The Public Benefits

What these data show is that the Hatch-Waxman compromise is both promoting competition—by making it easier, cheaper, and quicker for low-cost generic copies of pioneer medicines to enter the market—and providing limited incentives for innovation—by restoring part of the patent life lost by pioneer products due to FDA regulatory review. As a result, consumers are receiving the benefits of early access to low-cost generic copies and of an expanding stream of new, more precise, and more sophisticated medicines.

The Hatch-Waxman Compromise

How has the Hatch-Waxman compromise both promoted competition and preserved incentives for innovation? A little history helps to explain.

Prior to 1984, there were few generic copies of pioneer drugs that had been approved after 1962. The safety and effectiveness data supporting the approval of a post-1962 drug was considered to be trade-secret information that could not be used to approve generic copies. Apart from repeating the long, costly clinical studies performed by an innovator company, a generic applicant could obtain approval of a post-1962 drug only by using a literature-based (so-called "paper") New Drug Application (NDA), which was possible only when published scientific literature demonstrated a drug's safety and effectiveness.

To permit the approval of generic copies of all post-1962 drugs, the Hatch-Waxman compromise in effect revoked the trade-secret status of innovators' safety and effectiveness information. Instead of proving safety and effectiveness, a generic manufacturer was allowed to show only that its copy is "bioequivalent" to a pioneer product and FDA could rely on the pioneer's safety and efficacy data to approve the copy.

Bioequivalence means that a copy's active ingredient is absorbed at the same rate and to the same extent as that of the pioneer medicine. As a result of the 1984 law, generic manufacturers are able to avoid the huge cost (estimated at $500 million on average) of discovering and developing a new drug. It costs only a very small fraction of that amount for generic manufacturers to demonstrate bioequivalence—which is why they can market their copies at reduced prices.

The Hatch-Waxman compromise also helped generic manufacturers by overruling a 1984 Court of Appeals decision in the Bolar case. The Court had held that it constituted patent infringement for a generic company to manufacture and test a medicine before its patent expired even if its only purpose was to prepare a marketing application. In a unique exception to patent law, the Hatch-Waxman compromise allows generic manufacturers to use innovator medicines still under patent to obtain bioequivalency data for their FDA applications (a use that ordinarily would be a patent infringement) so they can be ready to market their copies as soon as the pioneer patents expire.

The 1984 law also sought to increase the number of generic copies by providing an incentive for generic manufacturers to challenge pioneer patents. The first generic manufacturer to certify to FDA that a patent on an innovator medicine is invalid or is not infringed by its product obtains 180 days of exclusive marketing rights if the copy is approved before the patent expires. During that 180-day period, FDA cannot approve any other copies.

To attempt to balance the generic provisions, the Hatch-Waxman compromise provided limited incentives to pioneer companies to help spur innovation. The law restores part of the patent life—but not all—lost by innovator products as a result of FDA review:

- A pioneer drug receives a half-day in restored patent life for every day the product is in clinical trials prior to FDA review.
- A pioneer drug receives day-for-day restoration of patent life for the time it is under review by FDA. However, the effective patent life of a drug cannot exceed 14 years, regardless of how much time is lost in clinical testing and review. And the total time restored is limited to no more than five years (even if more than five years is lost during drug development and review).

Innovator drugs introduced in the 1990s that obtained patent restoration enjoyed an average effective patent life of less than 11.5 years—substantially less than the 18.5 years enjoyed by inventors of other products. (The full patent term in the U.S., as with all member nations of the World Trade Organization, is 20 years from the date a patent application is filed with the Patent and Trademark Office.)

In addition to partial patent restoration, the Hatch-Waxman law provides that FDA is prohibited from approving generic copies of a pioneer drug for five years after approval of an innovator product in the case of new chemical entities and for three years in the case of other drugs and innovations in existing drugs. These exclusivity periods are to protect an innovator's data when there is no patent protection. The law also creates a procedure for litigating patent disputes before FDA approves an allegedly infringing generic copy.

Few Patent Disputes

Despite the generic industry's arguments to the contrary, data compiled by FDA conclusively show that, in the overwhelming majority of cases, generic applications have not raised or encountered any patent issues that have delayed their approval. The facts speak for themselves:

- From 1984 through January 2001, *8,259 generic applications* were filed with FDA.
- Of these applications, 7,781—*94 percent*—raised no patent issues.
- Only 478 generic applications—*5.8 percent*—asserted a patent issue, either challenging a patent's validity or claiming non-infringement of a patent.

Further research shows that:

- Only 58 court decisions involving just 47 patents have been rendered resolving generic challenges to innovator patents—*a tiny fraction* of the number of generic applications.
- Only 3 of the patent disputes settled between innovator and generic companies have reportedly been challenged by the FTC—*an infinitesimal percentage* of the applications.

A Heavy Burden to Justify Change

Even though the Hatch-Waxman compromise stimulates competition and provides limited research incentives, generic manufacturers are advocating major changes in the legislation. We believe that, in view of the balanced nature of the law, any proponent of change has a heavy burden to clearly demonstrate that change is necessary and would not upset the delicate compromise achieved in 1984. We do not believe this burden has been met with regard to any of the changes that have been proposed. Therefore, we strongly oppose such changes that would, we believe, unfairly skew the law in favor of generic manufacturers and impede the ability of the research-based industry to realize in a timely way the promises that the accelerating biomedical advances hold for patients in all parts of the world.

The generic industry has raised concerns in four areas in particular, which are addressed to various extents and in various ways in the Brown-Emerson bill, H.R. 1862. (See also the Schumer-McCain bill, S. 812.) The research-based industry is convinced that the changes sought by the generic industry would overturn some of the main trade-offs of the Hatch-Waxman compromise, as briefly described below. We would be pleased to discuss these and other such issues in more detail with any Member of the Committee or staff member who so desires.

Patent-Dispute Settlements: The generic industry has proposed to place limits on settling patent litigation between innovators and generic manufacturers that are different from the rules that apply to the settlement of other types of patent litigation. There is no need to amend the Hatch-Waxman compromise to deal with this issue. Settling cases is encouraged by the courts, it avoids the expenses of litigation, and it can create results that accommodate the interests of both parties.

Any settlements that are anti-competitive are subject to regulatory challenge under existing law. The actions of the Federal Trade Commission (FTC) in challenging some recent settlements demonstrate that the antitrust authorities are actively and adequately monitoring settlements between pioneer companies and generic manufacturers.

Orange-Book Listings: The generic industry would change the procedure by which innovator companies can litigate patent disputes prior to FDA approval of an allegedly infringing product. This would upset a major feature of the Hatch-Waxman compromise. The provision was intended to offset the loss by pioneer companies of trade-secret status for their safety and effectiveness data and the loss of patent rights that had been recognized in the Bolar case that was overruled by the 1984 law.

Prior to 1984, FDA approved a marketing application for a generic product even if the patent holder contended that the product would infringe its patent. Although patent holders could sue infringers, recovery of damages was questionable, particularly when the infringer was a small generic manufacturer that was potentially responsible for treble damages that accumulate during the patent litigation.

Under Hatch-Waxman, innovators are required to have their patents listed in the FDA *Orange Book,* and a generic applicant must file a "Paragraph IV certification" if it wants the agency to approve its application before the listed patent expires. A generic applicant may file such a certification only if it contends that the unexpired patent is invalid or would not be infringed by its product. The generic applicant must send a copy of the certification to the patent holder and the manufacturer of the innovator drug. If the patent holder sues for infringement within 45 days, FDA is automatically barred from approving the generic application for up to 30 months while the case is litigated.

The generic industry has complained that this process has been abused and has argued that the law should be changed to limit the patents that can be listed, such as only listing patents on active ingredients. The data presented earlier conclusively show that the process has not been abused as the overwhelming majority of generic applications—94 percent—have not raised or encountered any patent issues.

There is no sound rationale why a generic manufacturer should be able to avoid pre-approval patent litigation by making small changes from the marketed product, such as by changing the crystalline form, when the changed product still infringes an innovator's patent. Pre-approval patent litigation should be linked to a generic applicant's reliance on an innovator's safety and effectiveness data—that was one of the trade-offs in the Hatch-Waxman compromise.

If a generic product would both rely on an innovator's data and infringe one of the innovator's patents, pre-approval patent litigation should be allowed. Thus, any patent that covers a product that could be approved based on an innovator's data should be listed in the *Orange Book* to permit pre-approval litigation.

Thirty-Month Bar: The generic industry contends that, once the patent-dispute procedure is triggered as described above, FDA should not be automatically barred from approving a generic application for up to 30 months. The industry also con-

tends that innovator companies should be required to post a bond that a generic manufacturer could collect if it prevails in patent litigation.

Patent disputes involving generic drugs are a special case under the law because the Hatch-Waxman compromise overruled the *Bolar* case and permits generic manufacturers to develop and test a competitive product before its patent expires, thus barring patent holders from asserting their rights during this period. Such otherwise-infringing testing is not permitted in any other U.S. industry.

Since the 1984 compromise gave generic manufacturers a multi-year head start on getting to market by authorizing product-development that would otherwise constitute patent infringement, innovator companies were given the offsetting benefit of being allowed to litigate a patent before FDA approves the product.

If it were not for the Hatch-Waxman compromise, an innovator could sue a generic manufacturer when it begins product development and the litigation might well be concluded by the time a product is ready for FDA approval. The generic industry cannot reasonably claim the right to engage in development activity that normally would be considered patent infringement and at the same time assert that there should be no special rules governing the related patent litigation.

"Late-Listed" Patents: The Hatch-Waxman compromise requires that, if a patent has been issued at the time an NDA is submitted to FDA, the patent information must be included in the NDA. If a patent is issued after FDA approves an NDA, the patent information must be submitted to FDA within 30 days after the issuance of the patent for listing in the *Orange Book.*

If a patent is listed in the *Orange Book* within 30 days of issuance, it is treated the same as all other listed patents. The generic industry has argued that the pre-approval litigation process should not apply to patents issued when generic drugs are close to being approved. The generic industry refers to these as "late-listed" patents even though they are listed promptly after they are issued in accordance with the Hatch-Waxman compromise.

The purpose of the pre-approval litigation procedure is to protect innovator companies from the injury that would occur if generic manufacturers sell infringing products and are unable to pay the potentially large amounts that would be due at the conclusion of litigation. This rationale applies to all patents, regardless of when issued. Innovator companies should not be deprived of one of the important rights conferred by the Hatch-Waxman compromise simply because a patent was issued after a drug was approved or because the Patent and Trademark Office (PTO) was slow in processing a patent application.

There are sufficient protections in existing law against abuse of the pre-approval litigation procedure. For example, patents are issued only if the PTO determines that they meet the statutory standards; innovator companies are subject to criminal penalties if they knowingly make a false statement to FDA to obtain listing of a patent in the *Orange Book,* and the Federal Rules of Civil Procedure provide sanctions if an innovator files a frivolous or improper patent suit. Further, if a patent is truly late-listed—i.e., listed more than 30 days after it is issued—FDA's rules exempt generic applicants with pending applications from filing a certification regarding the patent.

DTC ADVERTISING

On DTC advertising, PhRMA strongly supports direct-to-consumer advertising of prescription medicines as currently regulated by FDA and opposes any further restrictions on this pro-patient, pro-health activity. Left sitting on pharmacy shelves, medicines don't do anyone any good. Unless they are prescribed for patients, prescription medicines cannot prolong life, ease pain, reduce disability or improve the quality of life. And unless medicines are prescribed and used, they will not generate the funds needed for private industry to continue to research and develop new and more effective medicines.

In 1997, FDA under the Clinton Administration issued guidelines that clarified the agency's broadcast requirements. FDA no longer required radio and television ads to contain voluminous information about a drug's side effects. Under the draft guidance, ads still have to list major health risks as well as side effects and must set forth four ways for consumers to receive additional information.

FDA's 1997 decision was in reaction to a policy that had generated ineffective and confusing advertisements. Prior to the guidance, FDA required that a brief summary of the prescribing information for a drug had to be included in all advertisements—including broadcast advertisements—that both named a prescription drug and stated its purpose. The brief summary is an FDA-approved document that advises physicians, in very technical language, how to appropriately use a drug. Be-

cause of its technical, scientific wording, this summary is very difficult for ordinary patients and consumers to understand.

In announcing the clarifying guidance in August 1997, then FDA Lead Deputy Commissioner Michael Friedman, M.D., said: "Today's action can help promote greater consumer awareness of prescription drugs." Robert Temple, M.D., Associate Director for Medical Policy at FDA's drug division, added that, under the new guidance, ads could inform consumers about new products they might not learn about through other means. As an example, he cited a new generation of antihistamines that do not cause drowsiness. "You need to be told by someone that those products are out there or you'll never know," he said.

Patients are now more actively involved in their own health care than ever before. The consumer movement and the information explosion have empowered patients to participate in these decisions. Armed with information, patients have become active partners with health-care professionals in managing their own health care and they are savvy consumers. Rather than remaining uninformed and relying entirely on an increasingly complex health-care system, patients are asking questions, evaluating information, and making choices.

Direct-to-consumer advertising provides a valuable resource for patients to obtain information about specific diseases and conditions, particularly in rural areas of the country where access to providers and health-care information may be difficult. Too often, many common yet serious conditions go untreated even though effective treatments are available. Affected individuals may not realize they have a health condition. Others are aware of their symptoms, but may not know that treatment is available. Patients suffering from chronic conditions may be dissatisfied with current treatment, but are unaware that different options are available with fewer side effects or easier dosing regimens.

Pharmaceutical advertisements raise awareness of conditions and diseases that often go undiagnosed and untreated. For example, the American Diabetes Association estimates that of the 16 million Americans who have diabetes, 5.4 million don't know it. One third of the people with major depression do not seek treatment and millions of Americans are unaware that they have high blood pressure. By informing people about the symptoms of such diseases and the availability of effective, non-invasive treatments, direct-to-consumer advertising can improve public health.

There are encouraging signs that this is happening:

- A survey by *Prevention* magazine found that, as a result of DTC advertising, an estimated 24.7 million Americans talked to their physicians about a medical condition they had never previously discussed with a doctor. In other words, millions of people who had suffered in silence were encouraged to seek help.
- A 1999 survey by FDA found that 27 percent of respondents asked their doctors about a condition they had not discussed before. These conditions ranged from diabetes and heart disease to arthritis and depression.
- In the two years that ads for a medicine for erectile dysfunction have appeared, millions of men have visited their doctors to request a prescription for the drug. For every million men who asked for the medicine, it was discovered that an estimated 30,000 had untreated diabetes; 140,000 had untreated high blood pressure, and 50,000 had untreated heart disease. These numbers are striking—and this is just one drug.
- A study by IMS Health, a health-information company, found that, in the one year after an advertising campaign for an osteoporosis drug began, physician visits by women concerned about the disease doubled.

A growing body of evidence suggests that consumers like DTC advertising. A 1999 survey by FDA found that those who liked these ads outnumbered those who did not by nearly two to one. Eighty-six percent said the ads "help make me aware of new drugs," while 62 percent said the ads helped them to have better discussions with their physician about their health. A survey by *Prevention* magazine found that 76 percent of respondents thought the DTC ads "help people be more involved in their health care" and 72 percent felt the ads "educate people about the risks and benefits of prescription medicines."

Advertising is only one source of user-friendly information available to consumers. Some 50 consumer magazines that deal with health care are published every month. The *Physicians' Desk Reference,* or *PDR,* once confined to doctors' offices, is now available in a consumer edition at pharmacies. Internet users can surf tens of thousands of sites dedicated to health-care topics. In fact, according to health-care consultant Lyn Siegel, about 25 percent of online information is health-related, and more than half of the adults who go on the web use it for health-care information. So, while DTC advertising is an important source of information for consumers, it is clearly not their sole source of information—even though it is the most accurate because it is regulated by FDA.

Critics contend that increasing expenditures on DTC advertising are driving up the price of drugs, but the amount spent by pharmaceutical companies on advertising has remained fairly constant and price increases have been relatively modest. As health care shifts from a physician-directed to a patient-directed system, companies are shifting the allocation of expenditures within their marketing budgets away from doctors to patients, although the distribution of free samples by pharmaceutical companies (provided to physicians for trial use by patients) continues to grow and remains by far the largest part of their advertising budgets.

And, while total pharmaceutical expenditures are rising, price increases have been in line with inflation in recent years. According to IMS Health, a health-information company, total drug expenditures rose 14.7 percent in 2000. Of that figure, only 3.9 percent of the increase resulted from price increases. Most of the increase in drug expenditures came from the increased *use* of prescription medicines, including the use of newer, more expensive, and more effective therapies. The increased use of prescription drugs is a healthy trend. Drugs not only save lives—they save money in many cases by reducing the need for alternative, more expensive care. They keep patients out of hospitals, out of nursing homes, out of surgery, out of doctors' offices—and on the job. Still, only 8.2 percent of every health-care dollar is spent on prescription medicines, compared to 32 percent on hospital care and 22 percent on physician and clinical services.

In summary, direct-to-consumer advertising helps to meet the increased demands of consumers for information about diseases and treatments. It fosters competition among products, which can improve the quality of care for consumers. Most important, DTC advertising can improve public health. It is intended to start a dialogue between patients and doctors. Often, the dialogue will not result in a physician prescribing the drug mentioned by a patient. But it will prompt a discussion that may lead to better understanding and treatment of a patient's condition. And, whatever happens, it is important to remember that it is a physician who ultimately decides whether a drug should be prescribed and, if so, which medicine is most appropriate for a particular patient.

RX/OTC SWITCHES

The issue has recently arisen as to whether a party other than a sponsor of a New Drug Application (NDA) can request that FDA switch a prescription medicine to over-the-counter (OTC) status. It has been a long-term policy of FDA that such a request can be made only by an NDA sponsor, or by another with its approval, through the submission of an NDA supplement with extensive data to support safe and effective OTC use with appropriate OTC labeling. PhRMA strongly supports this practice that has long been followed for good reasons.

There are compelling legal reasons against forced switches of prescription drugs. These reasons have been spelled out in submissions to FDA. Without elaboration in this testimony, such switches would violate the confidentiality provisions of the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and the Fifth Amendment to the U.S. Constitution.

The process of discovering and developing new medicines, and new uses for existing medicines, is risky, expensive, and time-consuming. It is undertaken principally by private companies at their own initiative through the investment of huge sums in research and development ($500 million on average for one drug). This process has led to enormous progress in preventing and treating disease and in improving public health.

The sponsor of an NDA has the most comprehensive and detailed knowledge of its drug and is in the best position to design, finance, and conduct additional studies necessary to evaluate the safety and effectiveness of the drug for OTC use and to prepare the appropriate OTC labeling. Every recent switch has been based on the development and submission of substantial amounts of data demonstrating that a prescription drug would be safe, effective, and properly labeled for OTC use.

Such data have been almost universally submitted through NDA supplements, which give manufacturers the opportunity to earn exclusivity rights established by Congress as an incentive to invest in the necessary research. The NDA holder is in the best position to take all of the relevant information into account and to decide whether and when to initiate a switch. Forced switches are being proposed by insurers seeking to shift costs to patients. These third parties lack the necessary data to determine whether a switch is appropriate and are not themselves proposing to conduct the extensive studies needed to support a switch. Rather, they are seeking switches on the basis of assertions, anecdotal evidence, and other flawed and incomplete data.

FDA would be acting arbitrarily and capriciously if it applied a lower standard to switches initiated by the agency itself or by third parties than it applies when an NDA sponsor seeks such action. Forced switches also would alter revenue streams and expose manufacturers to different product-liability risks than anticipated when they planned their research investments.

There are good reasons to retain the process that has been of great benefit to FDA, industry, and the public for many years. It is the process most likely to generate the needed data and to ensure that only drugs that are actually safe for over-the-counter use can be obtained without a prescription. Switches based on insufficient data could put the public at risk. In fact, the one time FDA initiated a switch without the active support of the NDA holder—for a bronchodilator almost 20 years ago—the agency quickly rescinded its decision after receiving numerous adverse comments.

If third parties were allowed to initiate switches, moreover, there likely would be an outpouring of such requests—and it would be difficult, if not impossible, for FDA to control the process and decide who should and should not be permitted to seek these changes.

FDA certainly plays a critical role in the drug-development process in general and in switching drugs in particular. If the agency believes that a drug is an appropriate candidate to be switched, it can consult with the NDA holder to determine whether there is an interest in such a change and in developing a study program to support an application for a switch. Industry has long cooperated with FDA on issues of mutual interest and is ready to do the same on this important issue. But forced switches would be unprecedented, would violate the rights of NDA holders, and could be detrimental to public health.

This concludes my written testimony. I would be pleased to answer any questions or to supply any additional materials requested by Members or Committee staff on these or any other issues.

Mr. DEAL. Thank you, Dr. Glover.

Mr. Downey.

STATEMENT OF BRUCE L. DOWNEY

Mr. DOWNEY. Thank you, Mr. Chairman.

At the outset I'd like to thank the committee for holding this hearing. I think it addresses some very important subjects and I hope to contribute to that dialog.

As the chairman noted, I'll be testifying not only on behalf of myself, but also on behalf of the Generic Pharmaceutical Association and its 150 members that provide virtually all the generic drugs in this country.

I have submitted a written statement. I would ask that that statement be made a part of the record before I expand on those remarks.

Mr. DEAL. Without objection.

Mr. DOWNEY. Thank you. I'd also like to thank Congressman Brown and Congressmen Emerson for introducing their legislation. I think that legislation has many very positive features that would help speed generic products to market and add considerable savings to American consumers and to Congressman Pallone for his legislation which, if enacted, would eliminate some of the artificial barriers that we confront state-to-state as we try to market our products.

It really is a privilege to be here today because this legislation that we're addressing, the Waxman-Hatch legislation, was transforming. It created an entire industry. It's saved consumers tens of billions of dollars over the last 15 years. It's increased the amount of investment in R&D from the pharmaceutical companies, the branded companies. And it's done all of this in the context of free markets where there is really little State or Federal participation

in that. It's all been done in the marketplace, which I think is a tremendous accomplishment.

On a personal level, it's also given me a very good job in an exciting industry, and I'm very pleased for that.

I would like to really respond to some of the questions that have been asked today and try to put or thoughts together to respond on several issues. First the patent process.

As we have discussion about the 180 days of exclusivity and patent settlements and the 30 month stay, it really glosses over what I think is the underlying problem. And the underlying problem I think is twofold. One, the process in which you obtain a patent is loaded in favor of patent issuance and many patents that are not patent worthy get issued. And second, we have a broad definition of what's patentable in the United States, such that ideas that I don't believe necessarily merit patents earn them.

I want first to talk about the process. As you go to the Patent Office to make an application, you make a submission, there's an examiner, there's no opponent. So there's no one saying to the examiner or the judge this patent should not be issued because or this idea is not patent worthy because. All of the disclosure is made by the proponent. And in that context, it shouldn't be surprising when billions of dollars, literally, are at stake. Many proponents push the envelop to the bursting point in advocating in favor of patentability in the absence of opponent advocating to restrict the patent. Unpatentworthy ideas obtain patent protection. So I think that basic system leads to some of the problems that we've tried to overcome.

Also, I think some of the ideas that we consider patent worthy in this country really shouldn't be. Things like formulation patents on how to use an active ingredient in combination with other compounds to deliver a dose to a patient. How to score the tablets so they can be broken in a certain way to titrate the dose. All of these ideas are patentable under current law, but in my view add very little to the intellectual capital of the country.

Given this situation it seems to me the 180 days of exclusivity is our only line of defense. It's that exclusivity which gives us in the generic industry the incentive to go out after the patents issued, attack that patent in a way to get our products to market earlier than the patent law would otherwise provide.

Those who would say the 180 days of exclusivity is not important aren't responsible to shareholders and to the public for the profitability of our firms. We invest literally millions of dollars in these patent challenges and we do so, as Dr. Glover pointed out, in the face of a presumption of validity of the patent and in face of a situation where if we launch the product in the market that's subject to the patent, we could be subject to treble damages. In a company of our size, even one of the largest generic companies, we would be bankrupt if we were to launch, say, a Prozac into the market, market it for a year or so, and ultimately lose the patent case.

And Prozac is a very good example, because recently we did challenge the patents on Prozac, and there were two; one that expired in February 2001 and one scheduled to expire in December 2003. The 30 months passed before we got to trial. We could have theo-

retically launched that product to market and subjected ourselves to treble damages prior to the final decision of the case.

We lost the first patent, the one that expires in 2001, and we would have been out of business. But we won the second patent, and as a consequence of winning that second patent we'll bring generic Prozac to market 30 months in advance of that patent expiry at a savings of literally $4 or $5 billion to the healthcare system.

We invested 5 or 6 years in that case. We invested with our partner in excess of $8 or $10 million. And we did it all in the face of a presumption of validity that we had to overcome to bring the product to market. Without the exclusivity, without the return on that investment, we would simply not have undertaken that process.

We at Barr have undertaken six and completed six patent cases. We've won two, we've lost two and we've settled two. And I want to take up the question of settlements, because it's not the settlement that keeps you out of the market, it's the patent. If the patent's valid, you can't launch the product in defiance of that patent without subjecting yourself to unacceptable risks.

In our settlements, for example, in both cases we'll be launching a product under license from the innovator into the market prior to the patent expiry. In one case, 10 years prior to patent expiry. So that settlement brought economic benefits to us, less than we would have earned if we had taken the case to trial and won but more than we'd have earned if we had gone to trial and lost. And I think it's very significant because both cases we settled the subsequent challengers lost. And I think in retrospect that shows the wisdom of the settlement and I think an essential part of the patent process to be able to settle cases in order to keep—or actually to bring products to market faster to provide the incentive for the cases and bring generic products to the consumer.

I have lots of other remarks that I'd like to make, but I think the stop sign is on, and I'll pass the mike and answer questions when everyone's finished.

[The prepared statement of Bruce L. Downey follows:]

PREPARED STATEMENT OF BRUCE L. DOWNEY, CHAIRMAN, BARR LABORATORIES, INC.

Mr. Chairman, members of the Sub-committee, thank you for the opportunity to testify. My name is Bruce L. Downey, and I am Chairman of Barr Laboratories, Inc., which has facilities in New York, New Jersey and Virginia and manufactures and distributes a wide range of prescription medicines for the treatment of diseases ranging from breast cancer to heart disease to depression. Barr Laboratories is a member of the Generic Pharmaceutical Association.

Today, I am speaking on behalf of the GPHA and its more than 140 member companies, which manufacture nearly all generic pharmaceuticals distributed in the United States today. No other industry has made, nor continues to make, the contribution to affordable health care that is made by a robust generic pharmaceutical industry.

I want to thank Chairman Bilirakis, Chairman Tauzin, Congressman Dingell and Congressman Brown for focusing on an issue that has such significance for our industry and for the American consumer. This is the first House-sponsored hearing in some time that has looked specifically at the value and contribution of generic pharmaceuticals to consumers, and how our industry makes a significant contribution to affordable healthcare.

Often, when industries come to Congress, they bring an agenda that would impose significant costs on American taxpayers. The generic industry comes before you today to discuss ways to create a direct and immediate benefit for consumers by reducing health care costs by billions of dollars. A strong generic industry will allow

the government to do much more for all Americans—particularly the elderly, underinsured and uninsured—for much less. The opportunity to create immediate consumer benefits, at no additional cost, deserves serious consideration.

As I intend to demonstrate in my testimony, the generic pharmaceutical industry has saved, and continues to save, consumers billions of dollars a year in prescription costs. The problem is, however, that the legislative balance that created significant annual savings for consumers has gradually been eroded.

In just the past week, the value of America's pharmaceutical industry has been in the spotlight, as articles in newspapers and magazines across the nation focused on the 20th anniversary of the AIDS crisis. Universally, these stories addressed two issues: the extraordinary power of pharmaceutical research and development; and the extraordinary financial burden that has been created by these life-saving pharmaceutical therapies.

I want to stress that the generic pharmaceutical industry recognizes the risks in the investment made by the brand pharmaceutical industry in new pharmaceutical therapies. We also recognize that the brand industry deserves to receive incentives for its innovation. In addition, the health of the generic industry is tied substantially to the health of the brand industry and our future is directly linked to the ability of the brand industry to innovate and to bring new therapies to market.

As always, however, in the nearly 20-year history of the generic pharmaceutical industry, the challenge continues to be rewarding innovation but assuring competition at the end of brand exclusivity. Both the House and Senate, through recently introduced legislation, have taken the first steps in an effort to restore that balance. We welcome these initial first steps, but we respectfully call upon Congress to do much more to preserve the consumer savings that result from a healthy brand and generic pharmaceutical industry.

Since its inception in 1984, with the implementation of the Drug Price Competition and Patent Term Restoration Act, (commonly called the Hatch-Waxman Act), the generic pharmaceutical industry has been responsible for saving consumers and taxpayers billions of dollars each year.

According to the Congressional Budget Office Report of 1998, generic pharmaceutical competition returns a minimum of $8-10 billion a year in savings into the pockets of American consumers. With pharmaceutical sales in the United States in excess of $138 billion in the past year, sales of generic medicines accounted for less than 10% of the total dollars, but accounted for nearly one out of every two prescriptions filled. In fact, when you rank the top five pharmaceutical companies on the basis of prescriptions dispensed, three of the top five are generic pharmaceutical companies: Watson, Mylan and Teva, all members of our association.

Interestingly, this savings has not come at the expense of innovation. According to the same CBO Report, "Between 1983 and 1995, investment in R&D as a percentage of pharmaceutical sales by brand name drug companies increased 14.7 percent to 19.4 percent. Over the same period, U.S. pharmaceutical sales by those companies rose from $17 billion to $57 billion."

The evidence is compelling. The underlying premise of the Hatch-Waxman Act works—consumers benefit if a proper balance is maintained between rewarding innovation and guaranteeing competition.

Unfortunately, the delicate balance struck by Congress in 1984 has gradually grown lopsided in favor of the brand pharmaceutical industry, hostile to the generic industry, and as a direct result, become a threat to the expansion of consumer savings. The reason is simple: the brand industry discovered years ago that competition is good for consumers but bad for their bottom line.

When Hatch-Waxman was implemented, the assumption was that the brand products would lose about 30% of their market, but would recover this loss through price increases. However, the introduction of a generic product often results in such a significant market share loss—as much as 80-90%—that the brand company is not able to recover its loss. After starting their own generic businesses, and implementing other strategies, it became clear to brand companies that the only way to succeed was to delay competition for as long as possible.

Additionally, laboring under the burden of significant expectations from the financial markets to maintain strong profits, brand companies have increasingly found that they are unable to generate a consistent pipeline of new products to meet profit and growth expectations. The investment in new product innovation continues, but the value of extending the market exclusivity of existing products is increasingly viewed as a prudent financial investment.

The results of this investment in delaying competition have been significant. Delays in the introduction of generic competition, combined with the nearly $3 billion spent annually on direct-to-consumer marketing for new products that often displace generic sales, have resulted in a stagnation of the growth of generic substi-

tution. Nearly two decades after Hatch-Waxman, generic substitution rates hover in the low 40% area, rather than the 50-65% that was predicted by many experts just a few years ago.

Since 1984, no less than a half dozen different acts of Congress have delayed the introduction of generic competition for specific products. According to a National Institute for Health Care Management (NIHCM) Foundation study issued earlier this year, the slow erosion of Hatch-Waxman through legislation, and the increasing exploitation of legal and regulatory loopholes in the Act, has extended anticipated market exclusivity from approximately 12 years to more than 18 years for some drug products.

The cumulative effect of these actions has resulted in extending product monopolies by almost 50%. With national prescription drug spending continuing to increase at an alarming rate, it is incumbent upon Congress to re-set the 1984 balance. In other words, its time to put the health of Americans first, with the challenge of reachieving the optimal balance of rewarding innovation and assuring public access of affordable medicines immediately at the end of brand exclusivity.

Over the past decade, as it has become clear to the brand industry that delaying competition is one sure bet to ensuring a healthy profit stream, the number of other gimmicks applied to extend the life-cycle of products nearing the end of their patent life has increased dramatically.

Certainly, the stakes in this game are high. Products representing annual sales of more than $37 billion are due to lose patent protection in the next five years. Many of these are the blockbuster names that we all know. To preserve their monopolies, brand companies have turned to such tactics as patent evergreening, citizen petitions, application of the automatic 30-month stay in patent litigation, application for pediatric exclusivity, and other techniques that delay generic approval or prevent timely introduction of generic competitors.

I would like to cite two recent examples of the techniques used to "game the system."

The cancer agent Taxol enjoyed nearly 8 years of market exclusivity. But tactics employed by the brand manufacturer, Bristol-Myers Squibb, resulted in a two-and-one-half year delay in generic approval.

Taxol, an anti-cancer agent, was originally discovered and developed by federal researchers over a thirty-year period. Although BMS testified before Congress in 1991 that the compound was neither patented nor patentable and, therefore, BMS would not have any intellectual property rights, BMS received several patents on certain methods of administration and stabilizing the compound following FDA product approval. Another egregious fact is that prior to the expiration of five years of product exclusivity granted under Hatch-Waxman, BMS unsuccessfully appealed to Congress for additional market protection.

In a complex series of legal maneuvers involving patent listings in the Orange Book, that followed, BMS was able to delay generic approval. Part of these delays resulted from the 30-month stay provision of Hatch-Waxman that automatically prevents approval of a generic product for this period, while patent litigation is underway. These tactics, assuming a modest generic penetration of only 50%, at a 50% price reduction, cost consumers more than $500 million.

Another recent example is the anti-anxiety drug, Buspar, which had annual sales of $700 million. The product was in its 14th year of market exclusivity, when the brand company, again Bristol-Myers Squibb, filed a surprise last-minute new patent on Buspar one day ahead of generic competition.

The last-minute patent sought to protect a metabolite created by digestion of the drug in the human body. Again, because of the patent filing, the company was able to invoke the 30-month stay of approval of a generic competitor. Although this listing was ultimately overturned, these tactics, assuming a modest generic penetration of only 50%, at a 50% price reduction, cost consumers more than $57 million.

Both of these examples highlight two issues that Congress must address. First, patent law allows the listing of any number of patents on drug products, making it impossible for generic competition to begin on a date certain, as long as the brand company can find some aspect of the product that can be patented. This issue is an area where Congress could make significant and immediate changes, simply by conforming U.S. patent law to that practiced throughout the world.

The second issue is that of the 30-month stay. Delay equates to profit preservation, so the brand company has much to gain by initiating patent litigation against the generic competitor. They face no financial or other penalty if the case is ultimately found to be groundless. But they do get an automatic extension of their exclusivity while the case is in review. The burden rests entirely on the generic competitor. Congress could address this deficiency in Hatch-Waxman by requiring the

brand holder to post a bond as part of any patent litigation. This would place them at risk for taking actions that have no other purpose than to delay competition.

These are only two examples of a systematic process of investing in legal and regulatory innovation to prevent generic competition. These types of abuses need to be curbed.

How can we work together to fix this problem, and increase both access and cost savings? I believe that the answer rests in the combination of encouraging the increased usage of generic medicines today and strengthening Hatch-Waxman to restore the balance first established in 1984. Each of these steps can generate billions of dollars in savings for America's health care system, while increasing access to medicines that can improve and prolong life.

I would like to briefly address both points.

First, I would like to address the potential and immediate savings that can result from increasing the utilization of generic medicines. The price difference between an equivalent generic product and its brand equivalent can be as much as 70-80%. A decade ago, the price differential between a brand product and an equivalent generic product was approximately $17. Last year, that price differential had grown to approximately $46.

According to a study published last September by Tim R. Covington, Executive Director of The Managed Care Institute at Samford University, "An increase of only 1% in the nation's generic prescription utilization rate (approximately 27 million scripts) would generate a payer savings of $1.3 billion each year." Action by Congress to encourage the maximum utilization of generic medicines in federal and state prescription drug programs, and to develop national educational programs that communicate the sameness, safety and savings of generic medicines would be an investment that could return significant and immediate value to taxpayers.

Estimates suggests that total pharmaceutical spending in the next decade will triple to more than $330 billion by 2010. Clearly, increased utilization of generic drugs represents the only immediate, significant opportunity to put the brakes on this runaway escalation of America's pharmaceutical bill.

Second, I am encouraged that Congress has begun the process of considering ways to restore the intended balance of Hatch-Waxman. While it is too early in the legislative process for the generic industry to unconditionally endorse any current proposal, we strongly support Congressional initiatives that represent meaningful and substantive reforms of Hatch-Waxman, and that restore the balance necessary to remove the barriers that delay the introduction of more affordable generic pharmaceuticals.

Proposals that have been introduced on the Hill have been criticized for being too pro-generic. If that is the case, then they must also be criticized for being too pro-consumer. The facts are simple: investment by brand industry innovation in the legal and regulatory arenas can carry less risk and more reward than new product development.

Working together, I am confident that our industry and members of the House of Representatives and the Senate can find ways to increase consumer savings by restoring balance to the competitive landscape.

The membership of GPHA has identified a number of areas where Hatch-Waxman reform would accelerate the introduction of more affordable generic medicines. These proposals include eliminating the 30-month stay component of patent challenges, and requiring brand manufacturers to post a bond if they challenge generic product applications.

We believe that these and other proposals would dramatically encourage the competition that saves consumers more than $10 billion a year in prescription drug costs. GPHA is committed to working with the Senate and the Congress to ensure that any legislative initiatives: preserve the intent of Hatch-Waxman; result in a balance between the interests of the brand and generic industries; and, create a vibrant competitive environment in which substantial pharmaceutical savings reach American consumers.

In summary, the brand and generic industry agree that affordable medicines are the key to longer, healthier and more productive lives. We also agree that innovation must be rewarded. But the generic pharmaceutical industry is unwavering in its belief that after the expiration of a fair and equitable period of patent protection and market exclusivity, consumers should be allowed to enjoy the benefits that competition creates in lower costs and increased access.

Let us work together with you to resolve the problems of dispensing medicines to all Americans, including the under-insured and uninsured, by promoting the increased usage of generic medicines and working to ensure the timely introduction of generic competition.

I am happy to answer any questions you might have.

Mr. DEAL. Thank you, Mr. Downey.
Dr. Delgado.

STATEMENT OF JANE L. DELGADO

Ms. DELGADO. Good afternoon. My name is Dr. Jane Delgado. I'm President, CEO of the National Alliance for Hispanic Health, known as the Alliance.

It's been very interesting for me to sit here, read my testimony and think I have so much more to say, but I only have 5 minutes.

I should let you know I was also the consumer member of the Edwards Commission, which worked to restructure the FDA in the late 1980's, early 1990's. So I'm very familiar with some of the issues that were raised. I'm also familiar with the saying "to tell the truth, the whole truth and nothing but the truth." And two out of three is not enough, so I will do all three and my daughter is here, and I'm here in front of you.

So let me tell you what our concerns are. One of the major concerns we have, and it's not in my testimony, is this whole discussion about generic and brand. And I raise it because of the issue that what we know about physical science is changing.

For example, in our community, Hispanics, many people know things about us. They know that we're overweight, they know that we're diabetic, but they didn't know that we have less heart disease than non-Hispanic whites. They didn't know that what we also do is we live longer than non-Hispanic whites. They didn't know we have less breast cancer. They also didn't know how the differences are in how we metabolize our drugs.

So when people say generics, I say generic for whom? The FDA will also be able to tell you that if you look at who participates in these clinical trials, there are very few people who represent the diversity in this Nation. And there are differences.

As Dr. Woodcock says "Well, you know, you can take one medicine and you can take another one and it's okay, and it's a little different for you and it's a little different for them." Well, that little difference can mean a big difference for a patient. And I think in terms of your constituents, they can tell you what has happened with them when they use drugs.

Constituents don't take drugs or medicines because one is cheaper, one is expensive. That may help. They take them because it works. If it's cheaper and it doesn't work for them, they're not going to take it. So please go back to the idea that we want things that work for the patient.

I want to move on to one of the important facts that we also think is important is the idea of information to consumers. Someone said well, you know, these consumers are coming in and they're asking the doctor "I'm diabetic, I want some Zoloft." And it's the wrong thing they're asking for. Well, we have changed our healthcare system from a physician hospital based system to one which is more patient driven and one which is more at home. And that patient should be congratulated for having the nerve to come in and ask for something, even if it's the wrong thing. And if the communication is incorrect, well great. What a great way to start a discussion. If we only talk to people who knew everything, we'd be very bored. We need new viewpoints, even mistakes to correct

them; that's why we're here because obviously some people are saying one thing, other people saying another thing, and we're trying to make more sense of it. But this idea of correcting or talking to a patient is something which is not part of our healthcare system, is driven too often by factors of cost.

I got this publication yesterday from the American Academy of Family Physicians, and it said "life balance from doctor-to-doctor. Tip One: Don't try to be too efficient. Take time to really listen to a couple of patient's stories a day. We need to be fed by our patients." That is where medicine is today, and that's why direct to consumer advertising is important.

If more people are getting more medicines, good, they're getting treatment. If we have generic and we have brand, let the decision be made by the healthcare provider and the patient, not by anyone else. Those are the challenges we face, because our system is changing.

And if you look at the way is science is ongoing, they will look back upon us and say "Can you believe those people thought that if you gave 100 people the same medicine, they were supposed to respond the same. Ha, ha, ha." They will laugh because in the future medicine's going to be tailored to the individual.

And as medicines change, what becomes law or the policies we develop have to be able to incorporate those changes. Medicine is not of the past, it is of the future. And those are the things that we as Hispanics are very concerned about.

We know that we are now 12 percent of the population of the United States, that's even though the Census didn't include the 3.5 million people in Puerto Rico. But we're there, 12 to 13 percent. For us there are differences.

We also know for people who are over 75 only 2 years ago the FDA started to record what was going on with them.

If you add all the groups for which we really don't have the specificity of data on drugs and their impact, you have most of your constituents, gentlemen.

So, thank you very much. I'll be open for questions later.

[The prepared statement of Jane L. Delgado follows:]

PREPARED STATEMENT OF JANE L. DELGADO, PRESIDENT AND CEO, NATIONAL ALLIANCE FOR HISPANIC HEALTH

Good morning. My name is Dr. Jane L. Delgado and I am President and CEO of the National Alliance for Hispanic Health (the Alliance). I am pleased to be here today to present the Alliance's perspective on pharmaceutical access and direct to consumer advertising. Before presenting these views, however, I'd like to provide you with a short background on who the Alliance is so that you may better understand our perspective and our reasons for being here today.

The Alliance is the oldest and largest network of Hispanic health and human service providers. Alliance members serve over 10 million (one in four) Hispanic health consumers annually. Our members are community-based organizations, provider organizations, government, national organizations, universities, for-profit corporations, and individuals. We have a bi-partisan board and three things make the Alliance unique: (1) belief in community-based solutions, (2) representation of all Hispanic groups, and (3) refusal of funding from alcohol or tobacco companies. We are a principled and strong organization.

To meet the needs of our communities, the Alliance operates state-of-the-art services in four program centers: Consumers, Providers, Technology, and Science. We develop national model community-based initiatives for service delivery in areas currently covering: cancer, environmental health, HIV/AIDS, prenatal care, substance abuse, tobacco control, and women's health. In addition, we directly reach

Hispanic health consumers nationwide by connecting them to local services and information (using zip code) through our

—National Hispanic Family Health Helpline (1-866-SU-FAMILIA),
—National Hispanic Prenatal Helpline (1-800-504-7081), and
—National Hispanic Indoor Air Quality Helpline (1-800-SALUD-12)which have bilingual (Spanish and English) information specialists.

As one of the organizations that established the field of cultural proficiency for health providers, the Alliance operates a significant support network for health professionals including training and education programs for cultural proficiency. We maintain and update a national database of 16,000 community health providers, representing the largest network of health providers serving Hispanic communities.

As the organization that established the first Hispanic on-line presence in 1991, the Alliance continues to foster cutting edge initiatives in science and technology. We operate hispanichealth.org and this year will unveil a redesign of the site that will include community health chats, training resources, and a portal to accurate health information that will continue the Alliance's role as the Hispanic community's trusted source for the best in health information.

An innovator in health science, the Alliance operates a national network of university-based researchers working with community-based organizations. Alliance research was the first to show over eight years ago that the Hispanic community was growing at a faster rate than Census predictions and would be the largest racial or ethnic minority group by the year 2000. Our research has challenged long held notions of health and well-being by showing that while Hispanics are more likely to be uninsured and in poverty, we also live longer than non-Hispanic whites. We have demonstrated the positive role of community, culture, family, and faith in a healthy life and the negative impact of some U.S. cultural norms on health and well-being.

Alliance research has also shown, that while Hispanics live longer than non-Hispanic whites, it is a life often marked by chronic illness and disease. Hispanics are more likely to suffer from diabetes, depression, asthma, and other chronic illnesses and diseases yet we live longer than non-Hispanic whites. Our chronic conditions benefit from early identification and a treatment plan that includes the appropriate pharmaceutical regimen. For this reason, full access to available pharmaceuticals and information made available through direct-to-consumer (DTC) advertising is a critical issue for the Hispanic community.

ACCESS TO PHARMACEUTICALS.

Hispanics are the group least likely to have regular access to health care services. More than one third (37%) of Hispanics are uninsured compared to 14% of non-Hispanic whites.[1] The impact is that about one-third of the uninsured reported no usual source of health care (38%), skipping a recommended medical test or treatment (39%), or not filling a prescription (30%).[2] This lack of access to health care, including pharmaceuticals, is a significant barrier for Hispanic communities. The picture for pharmaceutical access is further complicated by formularies and other administrative strategies that limit access to the full range of pharmaceutical products. This is of particular concern to Hispanic consumers as research has shown that a number of pharmaceutical products have a different metabolic pathway for Hispanics. Finding the right product with the least side effects requires access to the full range of pharmaceutical products in a given class. However, many Hispanic consumers find that while a pharmaceutical product that works well for a majority of the population is on their formulary, other products which work better for them may not be accessible. The goal of a responsible pharmaceutical policy should be to make the full range of approved pharmaceuticals available to all so that a medical rather than cost-limiting decision can be made between a doctor and patient. It is disturbing that the discussion on pharmaceutical policy has focused on pharmaceutical spending as a negative for the health care system. Quite the opposite, pharmaceutical products are the most cost effective sector of health care. Increased spending on pharmaceuticals is a sign of our evolving health system, which has less of a focus on hospitalization. With improved products coming to market and a healthy research base there are new alternatives for those currently without adequate treatment options.

[1] The Kaiser Commission on Medicaid and the Uninsured. Uninsured in America: A Chart Book. May 2000.
[2] Ibid.

The facts of increased pharmaceutical spending argue for a responsible and patient-based policy that will expand rather than limit access to pharmaceutical products.

More than two-thirds (71%) of increased spending on pharmaceuticals is a result of increased utilization. According to IMS Health, in 2000, total prescription drug spending increased 14.7 percent. Of that amount, only 3.9 percent represented price increases, the remaining 10.8 percent reflects the fact that more patients are getting new and better medicines. Also according to IMS Health, the rate of increase in drug spending in 2000 (14.7%) was substantially lower than the rate in both 1999 (18.8%) and 1998 (16%).[3]

Value of new prescription drugs explains increased utilization. Utilization of pharmaceuticals is increasing because untreated patients are coming in for treatment and patients have access to new and better medicines. In the 1990's, according to the industry trade association PhRMA, over 300 new medicines were made available to patients. These mean new and better options for patients. For example, in a study published in *The New England Journal of Medicine,* it was reported that in the 16 months following the introduction of antiretroviral therapy for HIV, there was a 43 percent decrease in hospital inpatient care. According to Samuel A. Bozzette, a physician with the Veterans Affairs San Diego Healthcare System, who headed the study, "The drugs are almost a perfect substitute for hospital care. We can afford them because, in fact, we were already spending the money on HIV care" in the form of hospitalization.[4]

Increased utilization is good news—decreases spending on more expensive treatments and means improved health care for consumers. Since the 1960s, spending on prescription drugs as a percent of total national heath expenditures has remained below 10%; with nearly four times as much spent on hospital care.[5] Pharmaceuticals remain the most cost effective segment of the health care industry. The real story of increased pharmaceutical spending is that patients are getting treated with improved regimens or untreated patients are getting treated before a more costly acute episode arises, leading to reduced spending on other more expensive health care treatments and improved patient satisfaction. For example, a recent study of patients with severely weakened hearts due to heart failure found that use of a new beta blocker, not only reduced deaths by 35 percent compared with patients given a placebo, it also sharply reduced hospital admissions, hospital stays and the use of tests and procedures in the hospital.[6] Another study published in *The New England Journal of Medicine* found that the use of ACE inhibitors for patients with congestive heart failure reduced mortality by 16%, avoiding $9,000 in hospital costs per patient over a three-year period. Considering the number of people with congestive heart failure, additional use of ACE inhibitors could potentially save $2 billion annually.[7]

Pharmaceutical innovation is critical to improved health care. The aging of the population means that chronic illness and disease in this country will increase. The most cost effective to this evolving health challenge is access to the full range of pharmaceutical products and development of new and improved products to avoid hospitalization and costly (in human and economic terms) impact of not treating chronic illness and disease early. For example, about 70% of seniors (28 million) now suffer from cardiovascular disease. If this trend continues, over 50 million elderly could face this disease by 2050.[8]

Access to Information. New research is showing that health care disparities among black, Hispanic, and white Americans cannot be explained wholly by disparities in income and health insurance coverage among these groups, but that other factors such as lack of information play a critical role. Indeed, a new study sponsored by the federal Agency for Healthcare Research and Quality (AHRQ) has found that **one-half to three-fourths of the disparities** observed in 1996 would have remained even if racial and ethnic disparities in income and health insurance were

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[3] IMS Health Reports. A 14.9% Growth in U.S. Prescription Sales to $145 billion in 2000. May 31, 2001.

[4] "Providing Antiretroviral Therapy for HIV Infection," *The New England Journal of Medicine,* Vol. 344, No. 11, March 15, 2001.

[5] Health Care Financing Administration, Office of the Actuary, National Health Statistics Group, 2001.

[6] Ron Winslow, "GlaxoSmithKline's Coreg Benefits Heart Patients in Two Big Studies," *The Wall Street Journal,* March 21, 2001.

[7] The SOLVD Investigators, *The New England Journal of Medicine,* Vol.325, No.5, pp.293-302, 1991; Walsh/America/PDS.

[8] Scott-Levin, Integrated Share of Voice Services IMSHEALTH/CMR, 2001.

eliminated.[9] Access to information is a critical piece in the access picture for Hispanic and other underserved communities.

DTC pharmaceutical advertising is a responsible approach of discussing benefits and risks. DTC pharmaceutical advertising is more in the model of public health patient education rather than the Madison Avenue tradition of advertising. Indeed, a survey by the U.S. Food and Drug Administration (FDA) found that as many consumers recalled seeing DTC ads that contained information about "benefits of the drug" (87%) as did seeing "risk or side effects" (82%).[10] The FDA plays a vital and appropriate role in ensuring the patient's concerns are primary in DTC advertising. Unlike other sectors of the health care market (e.g. dietary supplements, over-the-counter drugs), DTC pharmaceutical advertising is required to use a "fair balance" of potential risks and benefits in consumer-friendly language. In addition, print advertising must include a brief summary of product information and broadcast advertising must make reference to label information sources (toll-free number, print ad, web site) and encourage discussion with a health care professional. Furthermore, all advertising is submitted to the FDA at first use. This responsible approach to advertising is one that should be used as a model for other sectors of the industry whose advertising by focusing on benefits without adequate discussion of risks does little to empower and inform consumers.

DTC advertising helps health consumers recognize untreated disease. The $2.5 billion spent by the pharmaceutical industry of DTC advertising in 2000 is less than 10% of the $26 billion spent in 2000 by the industry on research on development. Furthermore, this spending has dramatically increased patients' awareness of and ability to recognize untreated disease. A survey by *Prevention Magazine* found that since 1997, DTC advertising has prompted an estimated 54.2 million health consumers in the U.S. to talk to their doctors about a medical condition or illness they had never discussed with their physician before. This is critical to the 50% (6-8 million) people with diabetes who are not being treated as well as individuals with a range of other untreated conditions for which treatments are available. Furthermore, the *Prevention Magazine* survey of DTC advertising and consumers found that one-third (33%) of patients using a prescription medication were reminded to take their medication by a DTC ad.[11] This compliance benefit is significant for many chronic illnesses and conditions that require long-term compliance with a treatment regimen.

DTC advertising encourages discussion between patients and health providers. Patient-provider communication is being improved with DTC advertising. A study conducted by Harris Interactive found that 64% of doctors thought DTC ads help educate and inform the public.[12] Furthermore, a 1999 FDA survey of DTC advertising found that 81% of patient's reported that their doctor welcomed their question about a drug as a result of DTC advertising.[13] In addition, the FDA study also found that 27% of people who spoke to their physician as a result of DTC advertising, talked to them about a previously undisclosed medical condition.[14] Also, of consumers who spoke to their physician as a result of DTC advertising, a majority (53%) of physicians discussed non-drug therapy with their patient.[15]

Health care is in transition from a physician-directed, hospital-based system to a patient driven, at-home system. Responsible DTC advertising is another tool that empowers consumers with information that includes both benefits and risks so that the consumer can make an informed choice. Unfortunately, much information for consumers available through the internet and other venues is not subject to FDA standards nor does it benefit from a balance or benefit and risk information found in responsible DTC advertising.

Our challenge is to maintain the information, rather than image, base of DTC advertising and carry-over the high standards employed in pharmaceutical DTC advertising to other health care product advertising.

Mr. DEAL. Thank you.

Mr. Golenski.

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[9] Weinick, Robin, et. al. "Racial and ethnic differences in access to and use of health care services, 1977 to 1996," *Medical Care Research and Review,* November 2000, No. 57 (Suppl. 1), pp. 36-54.

[10] FDA 1999 Survey, question 7.

[11] Prevention Magazine. International Survey on Wellness and Consumer Reaction to DTC Advertising of Prescription Drugs: 2001.

[12] Prevention Magazine. International Wellness and DTC Study. 2001.

[13] FDA 1999 Survey, question 7.

[14] FDA 1999 Survey, question 7.

[15] Prevention Magazine. International Wellness and DTC Study. 2001.

STATEMENT OF JOHN D. GOLENSKI

Mr. GOLENSKI. Thank you, Mr. Chairman. My name is John Golenski. I'm the Executive Director of RxHealthValue, a national coalition of consumer groups, labor unions, provider groups, business groups and employers, insurers and health plans, pharmacy benefit management organizations and academic researchers committed to improving American's access to health improving prescription drugs.

As you can understand, a deliberative body comprised of nearly 40 organizations will rarely arrive at a full consensus regarding any issue. Remarkably, our membership has achieved consensus regarding the recommendations that I'm offering about direct-to-consumer advertising of pharmaceutical drugs to consumers and patients. I believe the fact of these consensus recommendations indicates the fundamental importance of this issue for the members of RxHealthValue. It is our belief that this form of advertising affects the health and safety of American patients and consumers.

The tremendous increase in the extent of DTC advertising of prescription drugs since the FDA removed the requirement for the brief summary of risk information in 1997 is well documented. It is almost impossible to open a general news magazine or view a prime time television program or listen to the radio and not see or hear advertising for prescription drugs. Given that the prescribing physician is the decisionmaker regarding the use of these medications, it is all the more startling that so many resources are expended by drug manufacturers to affect the attitudes of consumers and patients.

Although there is little evidence currently available regarding whether consumer and patient attitudes affect physician choice in prescribing, no stakeholder in the health system and health economy has suggested that the impact of such advertising is insubstantial. Given the FDA's expressed interest in assessing the effects of DTC advertising, we expect more direct evidence of impact will be available in the near term future.

While we await the results of planned and pending studies on the effects of DTC advertising on attitudes, behaviors and medical outcomes of the consumers and patients, RxHealthValue members are concerned that risk information in particular is not adequately reflectively conveyed in DTC advertising.

One of our member organizations, AARP, recently conducted a survey of members to assess the impact of DTC advertising finding that nearly a third of those surveyed could not recall ever seeing risk information in the ads. Two-thirds of the survey population felt that the information presented in such advertising was not particularly helpful in assessing recommendations about whether to take prescription medications. This poses a serious safety risk to consumers and patients.

In our first recommendation to the FDA presented publicly 1 year ago at the National Press Club RxHealthValue emphasized the fundamental importance of protecting the safety of patients and consumers who are confronted with DTC advertising. Thus, RxHealthValue recommends that the Congress direct the FDA first to convene a task force of key stakeholders, including the pharmaceutical manufacturers who advertise prescription drugs, as well as

consumer groups, patient organizations, provider groups, payers and relevant experts to develop and test standards for information disclosure on DTC advertising.

Second, to more carefully define the concrete meaning of "fair balance" in disclosing benefits and risks of advertised medications to include disclosure of other appropriate therapies in addition to alternative medications.

And third, to further define "fair balance" to mean that full disclosure of risks and side effects be given equal print and air time as the description of benefits in the same communication.

RxHealthValue recommends that the Congress direct that the appropriate agencies of the Federal Government conduct on-going research to evaluate the effects of DTC advertising on the health of American consumers and patients. It is a given that many Americans appreciate the increased awareness of diseases and conditions and potential therapies which DTC advertising makes possible. It is also true that such advertising can obscure potential hazards of the pharmaceutical advertised and neglect the relative value of other forms of therapy. Only thorough, independent research can demonstrate the differential impact of such advertising upon the health choices of American patients and physicians.

In conclusion, the members of RxHealthValue applaud the committee for engaging this dialog about the effects of this increasingly pervasive influence on the therapeutic choices of American consumers and patients. We pledge our assistance in implementing any of the recommendations we have offered and thank the committee for this opportunity to comment. And we will be glad to answer questions.

[The prepared statement of John D. Golenski follows:]

PREPARED STATEMENT OF JOHN D. GOLENSKI, RXHEALTHVALUE

Mr. Chairman, Members of the Committee, I am John D. Golenski, Executive Director of RxHealthValue, a national coalition of consumer groups, labor unions, provider groups, business groups and employers, insurers and health plans, pharmacy benefits management organizations, and academic researchers committed to improving Americans' access to health-improving prescription drugs. (Our membership list is appended below.) As you can understand, a deliberative body comprised of nearly 30 organizations will rarely arrive at full consensus regarding any issue. Remarkably, our membership has achieved consensus regarding the recommendations I am offering regarding Direct-to- Consumer (DTC) advertising of prescription drugs to consumers and patients. I believe the fact of these consensus recommendations indicates the fundamental importance of this issue for the members of RxHealthValue. It is our belief that this form of advertising affects the health and safety of American patients and consumers.

The tremendous increase in the extent of DTC advertising of prescription drugs since the FDA removed the requirement for the "brief summary" of risk information in 1997 [1] is well documented.[2] It is almost impossible to open a general news magazine, view a prime time television program or listen to the radio and not see or hear advertising for prescription drugs. Given that the prescribing physician is the decision-maker regarding the use of these medications, it is all the more startling that so many resources are expended by drug manufacturers to affect the attitudes of consumers and patients. Although there is little evidence [3] currently available regarding whether consumer and patient attitudes affect physician choice in pre-

[1] Draft Guidance for Industry: Consumer Directed Broadcast Advertisements: Availability. *Federal Register* 1997; 62:43171.

[2] Findlay, Stephen. Prescription Drugs and Mass Media Advertising. NIHCM, Sept. 2000.

[3] Bero, Lisa A. & Lipton, Shira. Methods for Studying the Effects of Direct-to-Consumer Pharmaceutical Advertising on Health Outcomes and Health Services Utilization. (Paper to be presented at ASPE Conference on Methods to Assess Effects of DTC Advertising, May 30, 2001).

scribing, no stakeholders in the health system and health economy have suggested that the impact of such advertising is insubstantial. Given the FDA's expressed interest in assessing the effects of DTC advertising, we expect more direct evidence of impact will be available in the near term future.

While we await the results of planned and pending studies on the effects of DTC advertising on the attitudes, behaviors and medical outcomes of consumers and patients, RxHealthValue members are concerned that risk information in particular is not adequately or effectively conveyed in DTC advertising. One of our member organizations, AARP, recently conducted a survey of members to assess the impact of DTC advertising[4] finding that nearly a third of those surveyed could not recall ever seeing risk information in the ads. Two thirds of the survey population felt the information presented in such advertising was not particularly helpful in assessing recommendations about whether to take prescription medications. This poses a serious safety risk to consumers and patients. In our first recommendations to the FDA, presented publically one year ago at the National Press Club, RxHealthValue emphasized the fundamental importance of protecting the safety of patients and consumers who are confronted by DTC advertising.[5]

Thus, RxHealthValue recommends that the Congress direct the FDA:

- To convene a task force of key stakeholders, including the pharmaceutical manufacturers who advertise prescription drugs, as well as consumer groups, patient organizations, provider groups, payers and relevant experts, to develop and test standards for information disclosure in DTC advertising.
- To more carefully define the concrete meaning of "fair balance" in disclosing benefits and risks of advertised medications to include disclosure of other appropriate therapies in addition to alternative medications.
- To further define "fair balance" to mean that full disclosure of risks and side effects be given equal print and air time as the description of benefits in the same communication.

RxHealthValue recommends that the Congress direct that the appropriate agencies of the Federal Government conduct on-going research to evaluate the effects of DTC advertising on the health of American consumers and patients. It is a given that many Americans appreciate the increased awareness of diseases and conditions and potential therapies which DTC advertising makes possible. It is also true that such advertising can obscure potential hazards of the pharmaceutical advertised and neglect the relative value of other forms of therapy. Only thorough, independent research can demonstrate the differential impact of such advertising upon the health choices of American patients and physicians.

In conclusion, the members of RxHealthValue applaud the Committee for engaging this dialogue about the effects of this increasingly pervasive influence on the therapeutic choices of American consumers and patients. We pledge our assistance in implementing any of the recommendations we have offered and thank the Committee for this opportunity to comment.

Mr. DEAL. Thank you, sir.

Mr. Geiser.

STATEMENT OF THOMAS GEISER

Mr. GEISER. Mr. Chairman and members of the committee, I'm Thomas Geiser, General Counsel of WellPoint Health Networks. I'm here with Dr. Robert Seidman, our chief pharmacy officer who is also available to answer your questions today.

Three years ago Dr. Seidman wrote a letter to the Food and Drug Administration pointing out that the safety profiles of the prescription allergy drugs Claritin, Zyrtec and Allegra may have been candidates for a switch to over-the-counter status. He asked that the FDA consider his letter a citizen's petition for FDA to undertake the switch. On May 11, 2001 the FDA convened an expert advisory committee to determine whether Claritin, Allegra and Zyrtec were safe for OTC use. The FDA noted that the other conditions for OTC

[4] Foley, Lisa A. & Gross, David J. Are Consumers Well Informed About Prescription Drugs? The Impact of Printed Direct-to-Consumer Advertising. AARO: Public Policy Institute, April 2000.

[5] Policy Recommendations. RxHealthValue May 10, 2000.

use that laypeople could self diagnose allergies, that appropriate labeling could be prepared and that the products were effective to relieve the symptoms of allergic rhinitis, that is runny nose, itchy watery eyes had already been settled. What remained for the expert advisory committee to determine was that the drugs were safe for use by laypeople OTC.

After hearing testimony from two of the three drug manufacturers from WellPoint and from other interested parties for a full day, the expert committee voted overwhelming that each of the drugs was, indeed, safe for OTC use.

Most importantly, these products surpassed the safety profiles of drugs already available OTC for use in connection with allergies. More than 1000 combinations of antihistamine products that were once Rx are now available OTC. These first-generation products have more significant side-effects, including drowsiness, dizziness, blurred vision, and dry mouth than any of the second-generation prescription antihistamines. The FDA's expert advisory committee noted their superior safety profiles throughout the discussion at the hearing.

We were asked by this committee today to address the legal authority of the FDA to switch prescription drugs to OTC use as a result of a citizen's petition such as that provided by WellPoint. A number of comments submitted to the FDA in connection with the May 11 hearing questioned the FDA's authority to make such a switch, and therefore WellPoint has submitted to the FDA a supplement to our citizen's petition to address those comments. The text of the supplement's contained in my written statement, which I'd like to summarize for you.

The Food, Drug and Cosmetic Act and the FDA's implementing regulations make it clear that Congress gave FDA the expressed legal authority to compel a switch from Rx to OTC status. Under the statute drugs are to be marked OTC with adequate directions for use by the lay public, unless they're exempted from this requirement. Section 502(f) of the Act states that a drug is misbranded unless it bears adequate directions for use.

Section 503(b) in turn grants the FDA the authority to exempt prescription drugs from the adequate directions for use requirement when a drug is safe for use only under the supervision of a medical practitioner.

Viewed in combination, these sections show that Congress intended that all drugs, unless exempted, bear directions for use that permit the lay public to use the drug safely OTC.

Now within the framework where all drugs must be available OTC unless exempted, the Act also grants FDA the authority to switch a product to OTC use where the product no longer fits the prescription labeling exemption. Again, the statutory grant of this authority is very, very clear. Section 503(b)(3) provides that the Secretary may by regulation remove drugs subject to Section 505—that's the new drug application section—when the requirements of paragraph 1 of this subsection—that is the prescription labeling exemption—when such requirements are not necessary for the protection of the public health.

Based on the plain meaning of the statute, it's difficult for me to come to any conclusion other than that Congress intended to

grant the FDA the authority to perform the type of action we have requested. In addition, under its regulations, the FDA is actually required to make a switch when the agency finds that the exemption is no longer necessary to protect the public health. The regulation, like the statute, I believe is very clear and unambiguous. It reads "Any drug limited to prescription use shall be exempted from prescription dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health."

Furthermore, the regulation states that the proposal to switch may be initiated by the Commissioner or by any interested party.

We believe the plain meaning of both the statute and the regulations could not be more clear.

In conclusion, the Food, Drug and Cosmetic Act, under that Act the FDA clearly poses statutory authority to initiate a switch. And, in fact, under its own regulations the FDA is actually required to initiate the switch when the Rx only requirement is not necessary for the protection of the public health.

Mr. Chairman, Dr. Seidman and I would be happy to answer any questions the members of the committee may have.

[The prepared statement of Thomas Geiser follows:]

PREPARED STATEMENT OF THOMAS GEISER, GENERAL COUNSEL, WELLPOINT HEALTH NETWORKS, INC.

Mr. Chairman and members of the Committee. My name is Thomas Geiser and I am the General Counsel for WellPoint Health Networks, Inc. WellPoint Health Networks ("WellPoint") serves the health care needs of nearly 9.8 million medical and more than 40 million specialty members nationally through Blue Cross of California, Blue Cross and Blue Shield of Georgia, and UNICARE. I am pleased to have the opportunity to testify before you today regarding WellPoint's Citizen Petition to the Food and Drug Administration ("FDA").

Let me introduce to you Rob Seidman, PharmD, MPH, our Chief Pharmacy Officer. Three years ago, in 1998, as Vice President of Pharmacy for Blue Cross of California, Dr. Seidman wrote a letter to the FDA pointing out that the safety profiles of the prescription ("Rx") allergy drugs Allegra, Claritin, and Zyrtec made them candidates for a switch to over-the-counter ("OTC") status. He asked that the FDA consider his letter, which is appended to our testimony, a Citizen Petition for FDA to undertake the switch. Six months later, Dr. Seidman received a reply from the FDA, which said that it was studying the issue. Eighteen more months passed, and last June (2000) the FDA held a two-day hearing, at which Dr. Seidman testified, on the process of switching a variety of types of drugs from Rx to OTC status.

In May this year, the FDA convened a joint meeting of two expert advisory committees to determine whether Allegra, Claritin and Zyrtec were safe for OTC use. The FDA noted that the two additional conditions for OTC use—that lay people could self-diagnose allergies and use appropriately labeled OTC antihistamines safely without supervision of a licensed professional—had already been settled. What remained for the advisory committees to determine was that the drugs were safe for use by lay people OTC. After reviewing volumes of medical data collected over many years and hearing testimony from two of the three drug manufacturers, WellPoint, and other interested parties for a full day, the two committees voted overwhelmingly that each of the three drugs was, indeed, safe for OTC use. We have attached WellPoint's May 11 presentation to today's testimony for your reference.

In fact, these products surpass the safety profiles of drugs already available for use in the treatment of allergies OTC. More than 100 combinations of antihistamine products that were once Rx are now available OTC. These first-generation products have more significant side effects, including drowsiness, dizziness, blurred vision, and dry mouth, than any of the three leading second-generation prescription antihistamines. The FDA's advisory panels noted their superior safety profiles throughout discussion at the hearing.

We were asked by the Committee today to address the legal authority of the FDA to effectuate the conversion of prescription drugs to OTC use as a result of a Citizen Petition. A number of comments submitted to the FDA contested the FDA's author-

ity to make such a switch, and so WellPoint has submitted to the FDA a supplement to our Citizen Petition to address those comments. The text of that supplement is restated below and will constitute the bulk of my testimony.

Whether a switch is initiated by a manufacturer, the FDA, or a third party through a Citizen Petition, it is WellPoint's position that the FDA has express legal authority to compel a switch to OTC status from Rx if the FDA finds that a given drug or drugs meet the requirements NOT to be exempted from the labeling requirements for OTC drugs. Indeed, we would argue that the Food, Drug, and Cosmetics Act ("FDCA" or the "Act"), as amended, requires the FDA to make the switch. These arguments are outlined below.

SUMMARY

On July 22, 1998, WellPoint (through its subsidiary Blue Cross of California) submitted a Citizen Petition requesting that the FDA remove the prescription exemption for three second-generation antihistamines: Allegra® and Allegra-D® (fexofenadine), Claritin® and Claritin-D® (loratidine), and Zyrtec® (cetirizine). On May 11, 2001, the FDA convened the Non-Prescription Drugs Advisory Committee and the Pulmonary-Allergy Drug Advisory Committee for a joint meeting and vote on whether the above three allergy drugs were safe and effective for OTC status. *See* 66 Fed. Reg. 17,431 (March 20, 2001). The two committees voted overwhelmingly that the data presented demonstrated that the 2nd generation antihistamine products were safe and that adequate directions for use by the lay public can be developed for OTC use.[1]

Despite the overwhelming votes by the scientific expert advisory committees that the safety data fully support an OTC switch for these products, there have been comments suggesting that either the FDA does not have the legal authority to initiate a switch of its own accord, or that for reasons not related to safety and effectiveness, the agency should choose not to initiate such a switch. However, an analysis of both the FDCA and FDA's implementing regulations demonstrate that not only does the FDA possess the statutory authority to initiate a switch, but under the FDA's regulations the Agency is required to initiate a switch when it finds that "such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and [the Commissioner] finds that the drug is safe and effective for use in self-medication as directed in proposed labeling." *See* 21 CFR § 310.200. The FDA acknowledged as much in its April 5, 2001, Memorandum on the Advisory Committee Meeting to Discuss OTC Antihistamines when it stated that it interprets the FDCA to mean, "any drug that can be used safely over the counter should be."

For the reasons explained below, because: (1) the safety and effectiveness of these 2nd generation antihistamine drug products have been examined by a committee of scientific experts and by overwhelming majority were found to be safe and effective for OTC drug use; (2) the FDA clearly possesses the statutory and regulatory authority; and (3) there has been ample opportunity for substantive public input and comment, the agency should, without due delay, initiate a switch from Rx to OTC status for these 2nd generation antihistamine drug products since the Rx exemption from adequate directions for use is no longer necessary for the protection of public health.

I. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT ESTABLISHES A CLEAR MANDATE THAT ALL DRUG PRODUCTS MUST BE SOLD OTC UNLESS THEY MEET THE EXEMPTION CRITERIA FOR PRESCRIPTION CLASSIFICATION

Section 502(f) of the FDCA states that a drug is misbranded unless its labeling bears:

> (1) adequate directions for use; and
>
> (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users . . .
>
> *Provided,* that where any requirement of clause (1) is not necessary . . . [FDA] shall promulgate regulations exempting [the product].

21 U.S.C. § 352(f). This section was passed in the original 1938 Act in order to protect the public from drugs that did not clearly explain their usage or potential dangers and required all such drugs to bear labeling that the lay public could understand. Although the Act has undergone significant changes since its passage in

[1] The advisory committee's votes were 19-4 for Claritin and Zyrtec and 18-5 for Allegra.

1938, this provision has never been removed. FDA regulations have documented this interpretation by defining "adequate directions for use" as "directions under which the layman can use a drug safely and for the purposes under which it is intended." *See* 21 CFR § 201.5. Thus, under this provision of the Act, all drug products, unless exempt, are to be labeled OTC with adequate directions for use for the average consumer.

Section 503(b) of the Act provides a definition of an Rx drug and then authorizes the exemption from the OTC labeling requirement for Rx drugs. This section reads:

> A drug intended for use by man which—
>
> (A) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or
>
> (B) is limited by an approved application under section 355 of this title to use under the professional supervision of a practitioner licensed by law to administer such drug;
>
> hall be dispensed only upon a written prescription of a practitioner licensed by law to administer such drug . . .
>
> * * *
>
> Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the [adequate directions for use], if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription.

21 U.S.C. § 353(b). This section provides a classification structure for Rx drugs, grants an exemption from OTC labeling requirements, and authorizes separate Rx labeling for products dispensed upon the prescription of a licensed practitioner.

Viewed in combination, these two sections unequivocally demonstrate that Congress intended that all drugs, unless exempted, bear directions for use that permit the lay consumer to use the drug safely OTC. An analysis of the legislative history of the Act further supports this analysis.[2]

Although today most new drugs that are approved under section 505 of the FDCA are exempted from the adequate directions for use provision because they are found unsafe for use except under the supervision of a medical practitioner and thus have the "Rx Only" designation, this longstanding statutory scheme and classification system has (1) served as the foundation for development of product labeling, (2) despite many changes to the FDCA, has never been removed or questioned by Congress; and (3) is only being questioned by certain factions of the pharmaceutical industry in the effort to prevent wide access to the 2nd generation antihistamines.

II. THE FDCA IS CLEAR IN ITS GRANTING OF THIS AUTHORITY TO THE FDA

A. The FDCA Clearly and Unambiguously Grants the FDA the Authority to Remove Drugs Subject to Section 505 From the Prescription Labeling Requirements

Section 503(b)(3) of the FDCA grants the agency the clear authority to remove drugs that have been approved by the new drug application ("NDA") process from

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[2] Comments from the statement of Sen. Copeland shed light on what Congress was attempting to do, "There is no more common or mistaken criticism of this bill than that it denies the right to self-medication, or as the objector usually fit it, "You can't take an aspirin tablet with a doctor's prescription." Nothing could be further from the truth. The proposed law simply contributes to the safety of self-medication by preventing medicines from being sold as "cures" unless they are really cures . . . There must be plain and explicit directions for use, as well as warnings that in certain pathological conditions the use of drugs would not be safe . . . When public health cannot be protected otherwise, the bill authorizes control through licensing." 79 Cong. Rec. 4567 (1934) (*reprinted in,* CHARLES WESLEY DUNN, FEDERAL FOOD, DRUG, AND COSMETIC ACT: A STATEMENT OF ITS LEGISLATIVE RECORD 90 (FDLI 1987)). Sen. Copeland further stated, "It requires that all drugs bear explicit directions for use and appropriate warnings against their consumption by children or in certain disease conditions where the use is contra indicated and may be dangerous to health." *Id.* at 162.

Comments of Mr. Walter G. Campbell, Chief of the Food and Drug Administration of the Department of Agriculture, "But what is desired by this particular paragraph [requiring that the product bear the common name of the drug and the ingredients] and by others which impose restrictions on statements made about the remedial properties of the drugs is to make self-medication safe." *Id.*

the prescription labeling requirement where it is no longer necessary to protect the public health. It states:

> [FDA] may by regulation remove drugs subject to section 505 [i.e., NDAs] from the requirements of paragraph (1) of this subsection [the prescription labeling exemption] when such requirements are not necessary for the protection of the public health.

21 U.S.C. § 503(b)(3).

This section of the Act was added in 1951 by the Durham-Humphrey Amendment ("DH Amendment"). *See* ch. 578 § 1, 65 Stat. 648 (Oct. 26, 1951).[3] Congress passed the DH Amendment to give the FDA greater authority over the labeling of products which due to the circumstances of the time had created inconsistencies among similar or even identical products. Its stated dual purposes were to (1) protect the public from abuses in the sale of potent prescription drugs and (2) to relieve pharmacists and the public from unnecessary restrictions on the dispensing of drugs that are safe for use without the supervision of a physician. See Sen. R. No. 946 at 1, *reprinted in* 1951 U.S.C.C.A.N. 2454. The clear language of this statutory provision and its underlying purpose is applicable to the situation presented in the WellPoint petition, as it was to the situation that existed when the provision was promulgated in 1951. In the instant situation, pharmacists and the public should be and would greatly benefit from being relieved from unnecessary restrictions on the dispensing of drugs, i.e., the 2nd generation antihistamines that are safe for use without the supervision of a physician.

B. When the Statute's Plain Meaning is Clear and Unambiguous the Analysis Stops

Under the well-established laws of statutory interpretation, when the *statute is clear and unambiguous in its granting of authority,* there is no need to conduct any further analysis. That is the case in the instant situation. The FDCA clearly grants the agency the authority to remove the exemption from adequate directions for use. When the plain meaning of the statute is clear and unambiguous, the inquiry must end.

Chevron Step I—Under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.,* 467 U.S. 837 (1984), courts employ a two-step test in determining whether an agency has presented a permissible interpretation of a statute it administers. *See id.* at 842-43. First, courts consider the plain meaning of the statute. The plain meaning of a statute is derived from both the statutory language itself "as well as the language and design of the statute as a whole." *See K Mart Corp. v. Carter, Inc.,* 486 U.S. 281, 291 (1988); *Bethesda Hospital Ass'n. v. Bowen,* 485 U.S. 399, 403-405 (1988). If the court determines that Congress has spoken to the precise question presented by the parties, the court must give effect to the unambiguously expressed intent of Congress. *See Chevron,* 467 U.S. at 842.

Congress clearly and unambiguously granted FDA the authority to remove the prescription exemption when it said "[FDA] may by regulation remove drugs subject to section 505 . . ." It is difficult to imagine a more clear, concise, and unambiguous statement than section 503(b)(3) of the Act. The plain meaning of the statute makes it wholly unnecessary and inappropriate to look any further beyond the language of the statute.

C. Assuming Arguendo that the Statute is Ambiguous, the FDA's Interpretation is Followed as long as it is Reasonable

Chevron Step II—Although the statute is clear on its face, assuming for the sake of argument that section 503(b)(3) is ambiguous in its granting of authority, the FDA's regulations at § 310.200 are a reasonable and permissible interpretation of the statute.

If a court determines that Congress has not spoken to the precise issue because "the statute is silent or ambiguous with respect to the specific issue," the court advances to the second step of *Chevron. See Chevron,* 467 U.S. at 843. Under *Chevron* step two, the court determines whether the agency's answer is based on a permis-

[3] The 1938 Act had set up a new drug application process whereby manufacturers would submit an NDA and unless FDA objected to the application, it would be deemed approved. Thus, the DH Amendment was passed during a period where many new drug applications had become effective by the NDA process. In addition to these drug "approvals," large numbers of products came onto the market as "me-too" versions of drugs already marketed, where manufacturers concluded on their own that their products were "generally recognized as safe." As a result of this system, at the time of the DH Amendment, it was not unusual for numerous drug products, each with the same active ingredient, each bearing different labeling. In fact, it was not unusual for some products to be labeled as prescription while others with the same active ingredient were marketed as OTC.

sible construction of the statute. *Id. Chevron* step two is not invoked when the court first encounters a potential ambiguity:

> [G]iven that the judiciary remains the "final authority on issues of statutory construction," abdication of that authority and deference to an administrative construction is legitimate only where the court confronts a gap in the statute that cannot be bridged by traditional tools of statutory construction and which can properly be characterized as an express or implied delegation of authority by Congress to an agency.

See Abbott Lab. v. Young, 920 F.2d 984, 995 (D.C. Cir. 1990) (Edwards, C. J., dissenting o.g.) (citing *Chevron,* 467 U.S. at 843 n. 9).

If, however, the court advances to *Chevron* step two, the court must defer to the agency's reasonable interpretation so long as it does not conflict with the statute's plain meaning. *See K Mart,* 486 U.S. at 281. With respect to section 503(b)(3), although it is difficult to discern any ambiguity, to the extent there may be an ambiguity in the statute, the agency's regulatory interpretation in 21 CFR § 310.200 is clearly reasonable.

Given that statute is so clear and unambiguous on this issue it is not surprising that other comments have argued not that the statute does not grant FDA the authority, but rather that the statute does not really mean what it clearly says. Such arguments should be dismissed. Attempts have also been made to argue that the section is obsolete, or has been superseded. Such arguments are also without merit however, since Congress has several times made major alterations to the statute (including 1962, 1984, and 1997) which did not include or even contemplate removing this section. Further, whether an agency has used its power in the past has no bearing on whether it possesses that power in the first instance. *See Jones Et Ex. v. Alfred H. Mayer Co.,* 392 U.S. 409, 437 (1968); *Sanders v. Dobbs Houses, Inc,* 431 F.2d 1097 (5th Cir. 1970).

III. FDA'S IMPLEMENTING REGULATIONS GIVE IT CLEAR AUTHORITY TO REMOVE THE LABELING EXEMPTION FOR PRODUCTS THAT ARE SAFE FOR USE WITHOUT MEDICAL SUPERVISION AND IN FACT REQUIRE IT TO DO SO WHEN THE EXEMPTION IS NO LONGER NECESSARY

A. The FDA's Regulations Require the Agency to Switch a Product to OTC Status When Prescription Labeling Is No Longer Necessary for the Protection of Public Health and Authorize the Agency to Do So On Its Own Initiative

With a classification system where drugs are presumptively OTC, it is not surprising that the statute and FDA regulations permit the agency to switch a product from Rx to OTC status where Rx labeling is no longer necessary to protect the public health. In spite of several comments challenging this authority, not only does the statute permit FDA to make such an Rx to OTC switch, but the FDA's implementing regulations require that the FDA remove the prescription drug dispensing requirements when it finds the requirements are no longer necessary for the protection of public health. 21 CFR § 310.200 reads:

> [a]ny drug limited to prescription use [under the FDCA] shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling. A proposal to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(C) of the act may be *initiated by the Commissioner* or by any interested person. Any interested person may file a petition seeking such exemption, which petition may be pursuant to part 10 of this chapter, or in the form of a supplement to an approved new drug application

21 CFR § 310.200 (emphasis added).

This regulation is consistent with the FDCA's granting of this authority in section 503(b)(3) and the Act's presumption that drug products should be available to consumers OTC if medical supervision is not required.

Certain comments have stated that the Kefauver-Harris Drug Amendments ("KH Amendments") in 1962 fundamentally altered the FDCA so that section 503(b)(3) and its implementing regulations were rendered ineffective. This argument is belied by an examination of the history and timing of 21 CFR § 310.200. In fact, the regulation stating FDA shall switch products OTC when the agency finds the restrictions are no longer necessary was proposed in 1963, shortly after the passage of the KH Amendments. See 28 Fed. Reg. 1449 (February 14, 1963). This disputes any argument that the KH Amendments so altered section 503(b)(3) as to render them inoperative. Based on the final and proposed rule it is clear that FDA considered the

KH Amendments consistent with their authority to mandate an Rx to OTC switch. The final rule published on June 20, 1963 is substantially similar to that which remains today.

The provisions of the final rule published on June 20, 1963 are set forth below:

> Any drug limited to prescription use under section 503(b)(1)(c) of the act *shall be exempted* from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measure necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed from proposed labeling. A proposal to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(c) of the Act may be initiated by the Commissioner or by any interested person. Any interested person may file a petition seeking such exemption, stating reasonable grounds therefor, which petition may be in the form of a supplement to an approved new-drug application. Upon receipt of such a petition, *or on his own initiative at any time,* the Commissioner will publish a notice of proposed rule making and invite written comments. After consideration of all available data, including any comments submitted, the Commissioner may issue a regulation granting or refusing the exemption, effective on a date specified therein".

21 CFR § 130.101 (published at 28 Fed. Reg. at 6385 (June 20, 1963), (emphasis added).[4]

Thirteen years later, the FDA again opined on this regulation. In 1976, the agency published a final rule on the OTC review procedure found at Part 330. See 41 Fed. Reg. 32,580 (August 4, 1976). In the proposed rule the FDA outlined the two procedures "by which a prescription drug ingredient may lawfully be marketed for OTC use." See 40 Fed. Reg. 56,675 (December 4, 1975). In the preamble the agency explains:

> Prior to the OTC drug review, the procedures for obtaining approval to market a prescription ingredient as an OTC ingredient were by petition to the [FDA] following procedures set forth under § 310.200 . . . This procedure may be initiated by the Commissioner or by a petition from any interested person . . .

Id. Section 310.200 clearly grants the FDA the authority for the type of switch requested by WellPoint and arguments that it is an obsolete provision are not supported by the FDA's actions and preambles to its regulations. Moreover, the FDA's regulations were promulgated through notice and comment rulemaking. The final regulations were adopted without any substantive comments from the industry or public. The only comments have come forth recently, after the expert advisory panel voted that the 2nd generation antihistamines are safe and can be adequately labeled for OTC use.

B. The Regulations Do Not Require that A Manufacturer Consent to a Switch in a Product's Status from Rx to OTC

The regulations require a medical, scientific and factual based inquiry to determine whether Rx labeling is required for the protection of public health. Once these protections are no longer medically/scientifically justified, the regulations specify they should be removed. For this reason, the regulations do not require that a switch be initiated by the drug manufacturer or that the manufacturer agrees to the proposal. Although for obvious reasons in such a situation it is preferable that the manufacturer concurs with the switch, there is no basis in either the regulations or the statute for a manufacturer to be permitted to ignore a determination that Rx labeling is no longer necessary for the product. Clearly, the manufacturers of Allegra, Claritin and Zyrtec have a right to be heard and submit data on the issue, but it is the FDA and not the drug manufacturers who have the final say on whether a product is safe and effective or in this case whether is a product is safe and effective for self-medication. Both Schering and Aventis were unable to specifically identify any safety concern or study, whether contemplated or underway, to address a safety concern with respect to the OTC marketing of the products. Two expert scientific advisory committees have reviewed the data, evaluated the issues presented by Pfizer, Schering, Aventis and the FDA, and voted overwhelmingly that Allegra, Claritin and Zyrtec are safe for OTC use.

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[4] 21 CFR § 130.101 was re-codified by the agency in 1974 and is now § 310.200. See 39 Fed. Reg. 11,680 (March 29, 1974).

IV. THE COMMENTS ARE INCORRECT WHEN THEY CLAIM THAT REMOVAL OF THE EXEMPTION IS A DEPRIVATION OF PROPERTY

A. Companies May Possess a "Property Right" in Their Approval and Proprietary Data

Several comments have argued that drug companies possess a "property right" in the ownership of a drug's approval and the data contained in the NDA. This fact is not disputed. The issue is whether the switch in labeling from Rx to OTC would be considered a regulatory "taking." It is clear that no court has ever found a government "taking" in a regulatory switch of a product's marketing status from Rx to OTC. This seems logical since in most cases such a switch is desired by the drug manufacturer because such a switch may lead to further exclusivity[5] and/or increased sales.

The Supreme Court has treated the issue of whether a taking has occurred as "essentially an 'ad hoc, factual,' inquiry . . . [but] has identified several factors that should be taken into account when determining whether a governmental action has gone beyond 'regulation' and effects a 'taking'." *Ruckelshaus v. Monsanto Co.,* 467 U.S. 986, 1005 (1984). This examination entails inquiry into such factors as the "character of the governmental action, its economic impact, and its interference with reasonable investment-backed expectations." *Id.* A taking has been held to not only include an actually physical invasion of property but also an action the effect of which is to deprive the owner of all or most of his or her interest in the subject matter. *See United States v. General Motors Corp.,* 323 U.S. 373 (1945). The claim that a switch in regulatory status of a drug from Rx to OTC is a "taking" is a novel legal argument, but ultimately meritless.

B. The Comments are Mistaken in Their Belief that the Removal of the Prescription Drug Exemption Would Constitute a "Deprivation of Property"

As noted above, a "takings" claim here would be predicated on the belief that a change in marketing status from Rx to OTC would constitute a "deprivation of property." It may be helpful here to note initially what changes the agency could require in order to effectuate a change, and conversely what types of changes the agency cannot compel under a switch.

Changes that would be required:

- removal of Rx designation;
- proposed labeling for OTC use

The status quo (i.e., things that would not be changed):

- FDA's decision would have no effect on the validity of the patents or any other exclusivity on the product (i.e., generic competition would not be introduced);
- FDA's decision would have no effect on the price at which the product may be sold;
- FDA's decision would not require FDA to disclose trade secret or privileged information;

Although no court has ruled on this specific issue, an examination of other takings clause cases that are similar demonstrates that a takings claim in this case has no merit. In the *Ruckelshaus* case cited above, the Monsanto Company objected to the Environmental Protection Agency ("EPA") using its safety data to evaluate another application for registration. *Ruckelshaus* is easily distinguished from an Rx-to-OTC switch because in such a switch, the agency action does not involve using a company's "property right" for the benefit of another party. It is simply a change in the marketing status of the drug to be available without a prescription. Further still, in Ruckelshaus the Supreme Court determined that Monsanto, while possessing a property right in its data, did not have a takings claim where Monsanto was "aware of the conditions under which the data are submitted, and the conditions are rationally related to a legitimate Government interest, a voluntary submission of data by an applicant in exchange for the economic advantages of a registration can hardly be called a taking" *Ruckelshaus,* 467 U.S. at 1007. These "conditions" included the fact that the data could be used with out Monsanto's permission.

Similarly, a drug is marketed as an Rx drug only under certain conditions. If a drug no longer meets the conditions upon which an exemption from adequate directions for use was granted, it must be regulated as an OTC drug. As with Monsanto, this regulatory condition is well known by drug companies and often utilized to their benefit. Therefore, as in *Ruckelshaus,* it is no "taking" to change the regulatory status of a drug product, even if the drug company objects to the switch. To further

[5] At the May 11, 2001 Advisory Committee meeting, Agency staff clearly stated that no additional information would be essential for approval of the switch. Thus, the companies would not be eligible for three years of market exclusivity under Section 505(j)(5)(D)(iv).

support this position, it is also clear that the regulatory action has no effect on the companies' ability to market or sell the product. For these reasons it is clear that neither the character of the act, nor the economic impact, fit into the category of actions that would constitute a regulatory taking.

V. WHEN PROMULGATING REGULATIONS SPECIFICALLY RELATED TO THE REQUESTED REMOVAL OF THE PRESCRIPTION STATUS EXEMPTION, FDA IS NOT REQUIRED TO DISCLOSE INFORMATION THAT IS SUBJECT TO TRADE SECRET PROTECTION.

Comments have argued that under the APA, FDA must publicly disclose the data upon which any proposed rule is based. However, no trade secret data must be disclosed by FDA in order to promulgate a regulation removing the exemption from adequate directions for use. Of course, the general disclosure rules exempts the disclose of trade secret information.[6] It is well known that certain data and information in an NDA is trade secret protected.[7] However, these comments fail to note that much of the information contained in an NDA is not protected as trade secret information and in fact is disclosable under the Freedom of Information Act. *See* 5 U.S.C. § 552 *et seq.* Under 21 CFR § 314.430, the following information contained in an NDA is already made available to the public:

- the summary basis of approval;
- study protocols;
- adverse event reports;
- lists of inactive ingredients;
- assay methods; and
- correspondence and summaries of verbal communications with FDA.

Only information that qualifies as trade secret or commercial and financial information that is confidential is not able to be disclosed. This information would not be relevant in an Rx to OTC switch. What is most relevant here is primarily the adverse events reports concerning the three products. These reports demonstrate a low incidence of significant adverse reactions associated with the three drug products. FDA has reviewed the data and presented a summary of the data at the public advisory committee meeting held on May 11, 2001. This information is not trade secret protected.

Furthermore, what is relevant in this instance has already been narrowed by the agency. The agency has not raised any questions as to the effectiveness of the 2nd generation antihistamines for the relief of symptoms of allergic rhinitis. The only item at issue is whether the products are safe for OTC use. This is a much more limited inquiry than a full NDA approval. The issue of whether trade secret information needs to be disclosed in order to evaluate this matter has already been answered. The advisory committee members have fully examined the safety information provided by the agency and voted on May 11, 2001, by a overwhelming majority, that these products are safe for OTC use. This determination did not require the disclosure of trade secret information. There is no reason that FDA cannot promulgate its rulemaking without the disclosure of protected information. summary basis of approval;

VI. THE COMMENTS' CLAIM OF A LACK OF DUE PROCESS ARE INCORRECT IN THAT THE DUE PROCESS REQUIREMENT IS MET BY THE CITIZEN PETITION AND NOTICE AND COMMENT PROCEDURE

A. Section 505(e) of the FDCA Requires the FDA to Provide a Formal Hearing Only When the FDA is Seeking to Withdraw an NDA

Several of the comments to the docket claim that any "modification" of an NDA requires the agency to provide a formal hearing. However, the FDCA and the FDA's implementing regulations do not provide for a hearing for a "modification" of an NDA. In fact, both the statute and regulations provide for a hearing only when the FDA proposes to *withdraw* an NDA. The statute at section 505(e) states in pertinent part:

> [FDA] shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds . . .

21 U.S.C. § 355 (emphasis added). The statute then enumerates five different situations under which approval can be withdrawn. They are:

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[6] *See United States v. Nova Scotia Food Products Corp.* 568 F.2d 240, 251 (2d Cir. 1977) (the general rule is that an agency disclose scientific material that is the basis of a rule making, but there is "an exception for trade secrets or national security").

[7] *See* 21 CFR § 20.61 for FDA's definition of "trade secret" and "commercial or financial information which is privileged or confidential."

1. data shows that the drug is unsafe;
2. new evidence shows that the drug is not safe;
3. new information shows that the drug is not effective;
4. patent information was not timely filed; and,
5. the application contains an untrue statement of material fact.

Id.[8] If the FDA proposes to *withdraw* an NDA based on one of the above reasons, a formal evidentiary hearing is required. However, the statute does not require a hearing for a proposal to modify an application, i.e., a change from Rx to OTC status or for any other change to an application other than withdrawal. As the FDA is not proposing to withdraw approval of any of these products, section 505(e) is inapplicable.

B. Arguments that the Administrative Procedure Act ("APA") Requires a Formal Hearing are Incorrect and Further, Any Due Process Concerns Are Adequately Addressed In The Notice And Comment Procedure Utilized In This Process

Several comments have argued that the APA, 5 U.S.C. § 551 et seq., itself provides an independent source of authority for a hearing were the FDA to initiate a switch of a product from Rx to OTC. However, a close examination of the provisions of the APA and relevant case law demonstrate that this is not correct.

Assuming first that an NDA meets the requirements for a "license,"[9] section 558 of the APA provides that, "except in cases of willfulness or those in which public health, interest, or safety requires otherwise, the *withdrawal, suspension, revocation, or annulment* of a license is lawful only if, before the institution of agency proceedings therefor, the licensee has been given notice . . . and opportunity to demonstrate or achieve compliance with all lawful requirements." 5 U.S.C. § 558. Again it is clear that the switch of a product from Rx to OTC does not constitute the "withdrawal, suspension, revocation, or annulment" of a license. Therefore this provision of the APA is not applicable.

Under the APA an agency may act through either rulemaking or adjudicatory procedures. In adjudication, a formal hearing on the record is required. The adjudication procedures are defined in section 554 of the APA. The adjudication provisions apply, "in every case of adjudication *required by statute*." *See* 5 U.S.C. § 554(a) (emphasis added). However, the APA in itself "imposes no requirement of an adversary hearing before an agency, but only specifies the procedure to be followed when a hearing is required by some other statute." *See Conley Electronics Corp. v. FCC,* 394 F.2d 620 (10th Cir. 1968); *see also Democratic Nat'l Committee v. FCC,* 460 F.2d, 891, 912 (D.C. Cir. 1972) ("Since there is no requirement of a hearing under the Communications Act this section of the APA is clearly inapplicable"); *Joseph E. Seagram & Sons, Inc. v. Dillion,* 344 F.2d 497, 501 (D.C. Cir. 1965). Since the FDCA does not provide for a hearing in this instance, and in fact specifies that the agency may "by regulation," remove the prescription exemption, no hearing is required in this case.

In any event, issues of due process, and notice and comment are dubious since the Citizen Petition requesting this action has been pending for three years and no party can claim to not have had an opportunity for its voice to be heard. Moreover, there has been ample opportunity to provide input and comment through the public Advisory Committee meetings that have been held to hear discussion of the issues. One can only surmise what type of information the drug companies would provide at a hearing that has not already been provided to the agency. One wonders whether it is due process at issue or due delay. To the extent that due process is at issue, the notice and comment procedure that FDA is required to perform is sufficient to meet those demands.

In conclusion, under the Food, Drug, and Cosmetic Act and FDA's implementing regulations the FDA clearly possesses the statutory authority to initiate a switch and under FDA's regulations, the agency is **required** to initiate a switch when the Rx only requirement is not necessary for the protection of the public health. The statutory and regulatory scheme has been in effect for a very long time and has served to protect the health and safety of the public. The Advisory Committees fully evaluated the scientific evidence and overwhelmingly voted that Allegra, Claritin, and Zyrtec are safe and can be adequately labeled for use by the lay public.

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[8] FDA's regulations at 21 CFR § 314.150 provide a hearing only for situations where the agency has proposed to withdraw an application.

[9] A "license" is defined as "a whole or a part of an agency permit, certificate, approval, registration, charter, membership, statutory exemption or other form of permission." 5 U.S.C. § 551(8).

Blue Cross of California

Rob Seidman, Pharm.D., M.P.H.
Vice President
Blue Cross of California Pharmacy

July 21, 1998

3760 '98 JUL 22 A9:36

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services, Rm. 1061
5630 Fishers Lane
Rockville, MD 20857

Dear Sir or Madam:

The undersigned submits this petition under the Code of Federal Regulations, Food and Drug Administration, Title-21, section 10.30. This regulation provides that drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA determines the prescription requirements to be unnecessary for the protection of public health. By receipt of this letter, I am petitioning the FDA to make the following exemptions:

Currently, the Federal Food and Drug Administration (FDA) authorizes over 100 different antihistamine and antihistamine/decongestant combinations for over-the-counter (OTC) sale. Although considered safe and effective by the FDA, all OTC antihistamine and combination antihistamine/decongestant combinations are non-selective and have a more significant sedative and anticholinergic effect than the three leading prescription antihistamine and antihistamine/decongestant products. The safest antihistamine and antihistamine/decongestant combination medications are available only by a prescription and are described below:

Allegra (60 mg fexofenadine);

Allegra-D (60 mg fexofenadine, 120 mg pseudoephedrine);

Claritin (5 mg loratadine);

Claritin-D (5 mg loratadine, 120 mg pseudoephedrine);

Claritin-D 24 Hour (10 mg loratadine, 240 mg pseudoephedrine); and,

Zyrtec (5 mg cetirizine and 10 mg cetirizine strengths).

Maintaining Allegra/Allegra-D, Claritin/Claritin-D and Zyrtec as prescription drugs only, while their more dangerous antihistamine and antihistamine/decongestant alternatives are available without a prescription, deprives a majority of patients ready access to quality pharmaceutical care. This lack of access results in a greater incidence of side effects associated with the OTC alternatives adding considerable unnecessary medical costs to the health care system. The following information is provided to validate the petition and medical rationale for the conversion of Allegra/Allegra-D, Claritin/Claritin-D and Zyrtec to OTC status.

- Of the 3.5 billion health problems treated annually, almost 2 billion (or 57%) are treated with OTC drugs as primary or major adjunctive therapy. The current restrictions limiting OTC access to antihistamine and antihistamine/decongestant medications with a higher incidence of sedation and anticholinergic side effects is dangerous and costly.

98P-0610

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- Americans are 4 times as likely to purchase an OTC medication as they are to consulting a physician. Many patients can not afford the office visit associated with a physician's visit. The current restrictions precluding OTC access to antihistamine and antihistamine/decongestant medications with a lower incidence of side effects predisposes many patients to dangerous antihistamine and antihistamine/decongestant treatment options.

- Almost 60% of all dosage units consumed by patients are for OTC medications. The current restrictions precluding OTC access to antihistamine and antihistamine/decongestant medications with a lower incidence of side effects limits many patients to dangerous antihistamine and antihistamine/decongestant treatment options.

- Over 500 medical conditions are treatable with one or more OTC medications as the primary therapy or major adjunctive therapy. These conditions occur millions of times each year (e.g. cold, allergy, and nasal congestion). The current restrictions precluding OTC access to antihistamine and antihistamine/decongestant medications with a lower incidence of side effects predisposes many patients to dangerous antihistamine and antihistamine/decongestant treatment options for the self treatment of many of these conditions.

- Requiring that a patient schedule an office visit to obtain safe medications such as Allegra/Allegra-D, Claritin/Claritin-D or Zyrtec is an undue time and financial burden to the patient. Additionally, requiring a prescription for these safe antihistamine and antihistamine/decongestant combinations trivializes the patient-physician relationship.

- Based on recent historical precedent, the cost of the OTC versions of the drugs listed above will be 50% of the prescription drug cost.

Patients are seeking greater ownership of their health care and often prefer to self medicate when feasible. Of all the therapeutic classes of drugs available, the discrepancy in safety between the antihistamine and antihistamine/decongestant combinations available OTC compared to prescription Allegra/Allegra-D, Claritin/Claritin-D and Zyrtec is most pronounced. Based on the information provided above, please expedite the conversion of Allegra/Allegra-D, Claritin/Claritin-D and Zyrtec to OTC medication status.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition

Respectfully,

Robert C. Seidman, PharmD, MPH
Vice President
Blue Cross of California Pharmacy

cc: Douglas Schur, Vice President of Legal Services

Blue Cross of California

Rob Seidman, Pharm D., M.P.H.
Vice President
Blue Cross of California Pharmacy

July 23, 1998

4178 '98 JUL 24 A9:27
G.P.

Food and Drug Administration
Division of Management Systems & Policy
Dockets Management Branch
ATTN: Gloria Ortega
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Dear Ms. Ortega:

Pursuant to Section 10.30, Section C of the Food and Drug Administration, we are requesting an exception to provide an environmental assessment under Section 25.24. Since the medications we are wishing to convert from prescription to over-the-counter (OTC) are already widely used, the conversion from prescription to OTC status will not result in the introduction of any additional drug substances into the environment. We appreciate your waiving of the environmental assessment provision for this important petition.

Respectfully,

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Blue Cross of California

Rob Seidman, Pharm.D., M.P.H.
Vice President
Blue Cross of California Pharmacy

January 12, 1999

Director of Regulatory Affairs
Pfizer US Pharmaceutical Group
235 E. 42nd Street
New York, NY 10017-5755

Dear Sir or Madam:

On July 24, docket number 98P-0610/CP was filed with the Food and Drug Administration under the Code of Federal Regulations, Food and Drug Administration, Title-21, section 10.30. This regulation provides that drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA determines the prescription requirements to be unnecessary for the protection of public health. My letter specifically petitions the FDA to convert non sedating antihistamines to OTC regulatory status.

Currently, the Federal Food and Drug Administration (FDA) authorizes over 100 different antihistamines for over-the-counter (OTC) sale. Although considered safe and effective by the FDA, all OTC antihistamines are non-selective and have a more significant sedative and anticholinergic effect than the three leading prescription antihistamine products. Your safest antihistamine medications are available only by a prescription in the United States and are described below:

Zyrtec (cetirizine tablets and syrups)

Maintaining Zyrtec as a prescription drug only, while the more dangerous antihistamine alternatives are available without a prescription, deprives a majority of patients ready access to quality pharmaceutical care. This lack of access results in a greater incidence of side effects associated with the current OTC alternatives, adding considerable unnecessary medical costs to the health care system. The following information is provided to validate the petition and medical rationale for the conversion of Zyrtec to OTC status:

- Of the 3.5 billion health problems treated annually, almost 2 billion, or 57%, are treated with OTC drugs as primary or major adjunctive therapy. The current restrictions limiting OTC access to antihistamine medications with a higher incidence of sedation and anticholinergic side effects is dangerous and costly.

- Americans are 4 times as likely to purchase an OTC medication then they are to consult a physician. Many patients can not afford the office visit associated with a physician's visit. The current restrictions precluding OTC access to antihistamine medications with a lower incidence of side effects predisposes many patients to dangerous antihistamine treatment options.

- Almost 60% of all dosage units consumed by patients are for OTC medications. The current restrictions precluding OTC access to antihistamine medications with a lower incidence of side effects limits many patients to dangerous antihistamine treatment options.

98P-0610

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- Over 500 medical conditions are treatable with one or more OTC medications as the primary therapy or major adjunctive therapy. These conditions occur millions of times each year (e.g. cold, allergy, and nasal congestion). The current restrictions precluding OTC access to Zyrtec, which has a lower incidence of side effects, predisposes many patients to dangerous antihistamine treatment options for the self treatment of many of these conditions.

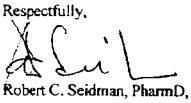
- Requiring that a patient schedule an office visit to obtain safe medications such as Zyrtec is an undue time and financial burden to the patient. Additionally, requiring a prescription for these safe antihistamines trivializes the patient physician relationship.

- Zyrtec has been reviewed and approved by the Canadian and European equivalents to the FDA as direct to OTC approvals, bypassing the prescription requirement process.

Patients are seeking greater ownership of their health care and often prefer to self medicate when feasible. Of all the therapeutic classes of drugs available, the discrepancy in safety between the antihistamines available OTC compared to prescription Zyrtec is most pronounced. Based on the information provided above, it is logical that Zyrtec be immediately converted to OTC medication status.

Pfizer's direct to OTC approvals for Zyrtec in Canada and Europe are particularly relevant to my petition. At this point in the FDA review process, it is appropriate that the United States Food and Drug Administration have access to your New Drug Submissions in Canada and Europe for the OTC forms of Zyrtec. To help ensure a timely review of my petition, please expedite a summary of these documents to my attention within 30 days of your receipt of this letter.

Respectfully,



Robert C. Seidman, PharmD, MPH
Vice President
Blue Cross of California Pharmacy

CC: Douglas Schur, Esquire, WellPoint Health Networks
Andrea Masciale, Regulatory Policy Division, FDA

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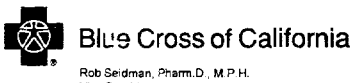

Rob Seidman, Pharm.D., M.P.H.
Vice President
Blue Cross of California Pharmacy

January 12, 1999

Director of Regulatory Affairs
Hoechst-Marion Roussel
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64137-1405

Dear Sir or Madam:

On July 24, docket number 98P-0610/CP was filed with the Food and Drug Administration under the Code of Federal Regulations, Food and Drug Administration, Title-21, section 10.30. This regulation provides that drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA determines the prescription requirements to be unnecessary for the protection of public health. My letter specifically petitions the FDA to convert non sedating antihistamines to OTC regulatory status.

Currently, the Federal Food and Drug Administration (FDA) authorizes over 100 different antihistamine and antihistamine/decongestant combinations for over-the-counter (OTC) sale. Although considered safe and effective by the FDA, all OTC antihistamine and combination antihistamine/decongestant combinations are non-selective and have a more significant sedative and anticholinergic effect than the three leading prescription antihistamine and antihistamine/decongestant products. Your safest antihistamine and antihistamine/decongestant combination medications are available only by a prescription in the United States and are described below:

Allegra (60 mg fexofenadine)

Allegra-D (60 mg fexofenadine, 120 mg pseudoephedrine)

Maintaining Allegra and Allegra-D as prescription drugs only, while their more dangerous antihistamine and antihistamine/decongestant alternatives are available without a prescription, deprives a majority of patients ready access to quality pharmaceutical care. This lack of access results in a greater incidence of side effects associated with the current OTC alternatives, adding considerable unnecessary medical costs to the health care system. The following information is provided to validate the petition and medical rationale for the conversion of Allegra and Allegra-D to OTC status:

- Of the 3.5 billion health problems treated annually, almost 2 billion, or 57%, are treated with OTC drugs as primary or major adjunctive therapy. The current restrictions limiting OTC access to antihistamine and antihistamine/decongestant medications with a higher incidence of sedation and anticholinergic side effects is dangerous and costly.

- Americans are 4 times as likely to purchase an OTC medication then they are to consult a physician. Many patients can not afford the office visit associated with a physician's visit. The current restrictions

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precluding OTC access to antihistamine and antihistamine/decongestant medications with a lower incidence of side effects predisposes many patients to dangerous antihistamine and antihistamine/decongestant treatment options.

- Almost 60% of all dosage units consumed by patients are for OTC medications. The current restrictions precluding OTC access to antihistamine and antihistamine/decongestant medications with a lower incidence of side effects limits many patients to dangerous antihistamine and antihistamine/decongestant treatment options.

- Over 500 medical conditions are treatable with one or more OTC medications as the primary therapy or major adjunctive therapy. These conditions occur millions of times each year (e.g. cold, allergy, and nasal congestion). The current restrictions precluding OTC access to Allegra and Allegra-D, which have a lower incidence of side effects, predisposes many patients to dangerous antihistamine and antihistamine/decongestant treatment options for the self treatment of many of these conditions.

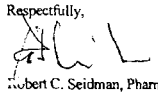
- Requiring that a patient schedule an office visit to obtain safe medications such as Allegra and Allegra-D is an undue time and financial burden to the patient. Additionally, requiring a prescription for these safe antihistamine and antihistamine/decongestant combinations trivializes the patient physician relationship.

- Allegra and Allegra-D as exclusive ingredients and in their decongestant combinations have been reviewed and approved by the Canadian and European equivalents to the FDA as direct to OTC approvals, bypassing the prescription requirement process.

Patients are seeking greater ownership of their health care and often prefer to self medicate when feasible. Of all the therapeutic classes of drugs available, the discrepancy in safety between the antihistamine and antihistamine/decongestant combinations available OTC compared to prescription Allegra and Allegra-D is most pronounced. Based on the information provided above, it is logical that Allegra and Allegra-D be immediately converted to OTC medication status.

Hoechst-Marion Roussel's direct to OTC approvals for Allegra and Allegra-D in Canada and Europe are particularly relevant to my petition. At this point in the FDA review process, it is appropriate that the United States Food and Drug Administration have access to your New Drug Submissions in Canada and Europe for the OTC forms of Allegra and Allegra-D. To help ensure a timely review of my petition, please expedite a summary of these documents to my attention within 30 days of your receipt of this letter.

Respectfully,



Robert C. Seidman, PharmD, MPH
Vice President
Blue Cross of California Pharmacy

CC: Douglas Schur, Esquire, WellPoint Health Networks
Andrea Masciale, Regulatory Policy Division, FDA

Petition to Convert Claritin®, Allegra® and Zyrtec® to OTC Status

Robert Seidman, PharmD, MPH
Chief Pharmacy Officer
WellPoint Health Networks

FDA Pulmonary and OTC
Advisory Committee Meeting
May 11, 2001

WELLPOINT

Why I am here before you today.

WELLPOINT

History

- Blue Cross of California, a subsidiary of WellPoint Health Networks
  - Filed a Citizen Petition with FDA on July 22, 1998 under 21 CFR 10.30
  - Requesting that 2nd generation antihistamines and antihistamine/decongestant combinations be switched to over-the-counter status
    - Claritin®, Claritin-D®
    - Allegra®, Allegra-D®
    - Zyrtec®

WELLPOINT

Status of Petition

- No FDA decision
  - Petition pending for almost 3 years
- January 1999
  - FDA letter from Dr. Woodcock
    - Petition presents complex issues
    - FDA needs more time to evaluate
- June 2000
  - FDA hearing to review Rx to OTC process
- May 2001
  - FDA hearing to discuss the WellPoint petition

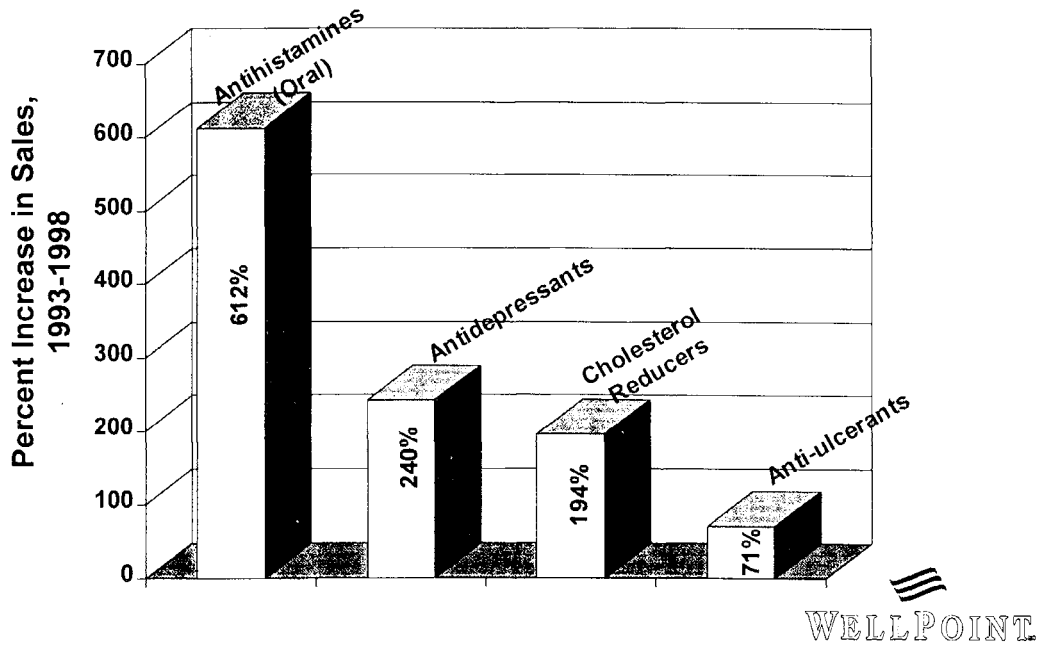
WELLPOINT

Why Did WellPoint Submit the Petition?

- Patients are seeking greater ownership and control over their healthcare;
- Prefer to self-medicate where appropriate and feasible;
- More convenient for patients;
- Patients can decide when they need to use antihistamines and antihistamine/decongestant combinations;
- Already over 100 different antihistamines and antihistamine/decongestant combinations OTC; and
- Rising cost of Rx drugs is making it difficult to provide an affordable, broad-based prescription benefit.

WELLPOINT

Recognition of the Problem



WELLPOINT

Why Are These Second Generation Antihistamines Prescription Drugs?

- Durham-Humphrey Amendment to Federal Food, Drug and Cosmetic Act (1951)

  A drug is expected to be made available without a prescription if, by following the labeling, consumers can use it safely and effectively without professional guidance.

WELLPOINT

Second Generation Antihistamines Meet Requirements for OTC Switch

- Can the condition be adequately self diagnosed? Answer - Yes
- Can the condition be successfully self-treated? Answer - Yes
- Is the self-treatment product safe and effective for consumer use, under conditions of actual use? Answer - Yes

WELLPOINT

2nd Generation Antihistamines

- Effective for relieving symptoms
  - Runny nose, sneezing, itching of the nose or throat and itchy, watery eyes
- Less side effects than 1st generation antihistamines currently available OTC
  - Less sedation (drowsiness)
  - Less anticholinergic effects

    (dizziness, blurred vision, dry mouth, etc.)

WELLPOINT

Evidence Report: Efficacy and Toxicity of Selected 1st and 2nd Generation Antihistamines

Jack Kern, Pharm.D.
Assistant Professor of Clinical Pharmacy
University of Southern California School of Pharmacy

Methods

- Literature
  - Identify all RCTs with selected antihistamines (reference librarian)
  - Reject/accept references
    - Screen titles, abstracts and references
- Build evidence tables
  - Significant factors!
- Build shrinkage plots (statistician)
- Discussion and understanding

Meta-Analysis Summary of Global Efficacy

Treated Group (n)	Comparison Group (n)	Number of Studies	Overall Effect Size	95% Confidence Interval	p value
Cetirizine 10 mg (384)	Placebo (378)	7	0.24	0.17-0.31	<0.001
Loratadine 10 mg (746)	Placebo (744)	11	0.21	0.16-0.26	<0.001
Cetirizine (Children) (193)	Placebo (197)	3	0.26	0.16-0.36	<0.001
Cetirizine 10 mg	Loratadine 10 mg	3	0.15	0.05-0.25	<0.05
Chlorpheniramine (199)	Terfenadine (203)	5	0.05	-.02-0.12	>0.05

Meta-Analysis Summary of Sedation

Treated Group (n)	Comparison Group (n)	Number of Studies	Overall Effect Size	95% Confidence Interval	p value
Chlorpheniramine (219)	Placebo (217)	6	0.17	0.1-0.24	<0.001
Cetirizine 10 mg (766)	Placebo (756)	9	0.06	0.01-0.11	<0.05
Cetirizine (Children) (163)	Placebo (160)	3	0.05	0.01-0.09	<0.02
Loratadine 10 mg (727)	Placebo (714)	11	0.0	-.02-0.02	>0.05

Conclusions

- The quality of these studies is high
- 2nd generation antihistamines are as *effective* as the 1st generation products
- 2nd generation antihistamines are *safer* than the 1st generation products

Cost-Effectiveness of Converting Non-Sedating Antihistamines from Rx to OTC Status

Michael B. Nichol, Ph.D., Patrick Sullivan, Ph.D. (cand.)
University of Southern California School of Pharmacy

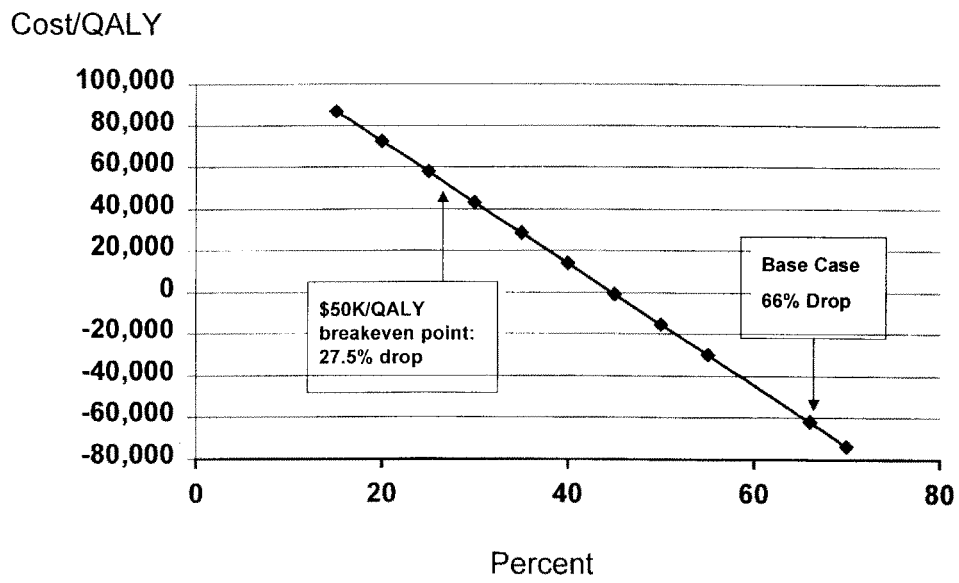
- Decision-analytic model
- Perspective: Societal
- Period: One year
- Cohort: Adult population in the U.S.
- Comparison: Prescription loratadine vs. over-the-counter loratadine
- Impact: Effects of sedation on motor vehicle accidents
- Output: Incremental cost per quality-adjusted life year

Base Case Results

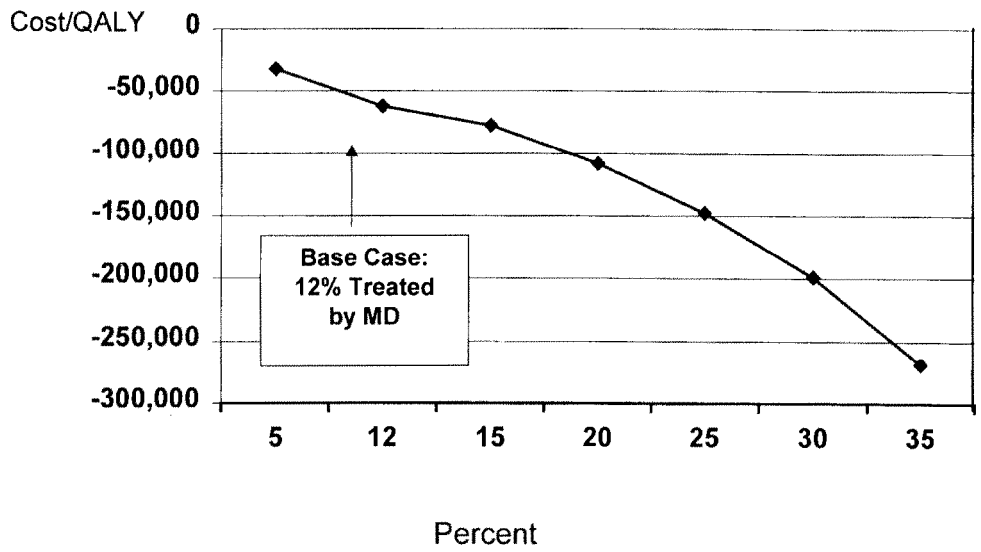
- **The Incremental Cost-Effectiveness Ratio (ICER) for the base case analysis is a *savings* of more than $62,000 per quality-adjusted life year**

- **Using the same base case values, an alternative estimate produced a *savings* of more than $98,000 per life year saved**

ICER Sensitivity Analysis: Percent Drop in Non-Sedating Price After OTC Conversion



ICER Sensitivity Analysis: Percent of Patients Treated by MD



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Conclusions

- Preliminary evidence suggests that converting non-sedating antihistamines to over-the-counter status would be *cost-saving* to society as a result of reductions in motor vehicle accidents

- Additional factors should be incorporated into a final model:
  - Inappropriate treatment with OTC non-sedating antihistamines
  - Modeling effect of OTC availability on price and demand
  - Refining incremental QALY improvements due to availability of non-sedating antihistamine
  - Impact on workplace productivity

Precedent for an FDA Initiated OTC Switch

- FDA initiated the OTC switch of Alupent® (metaproterenol) inhaler in 1982
- FDA did not seek input from an expert advisory panel or the public before permitting the drug to be marketed as an OTC drug product
- FDA received comments and public criticism from physicians who felt they should have been consulted prior to the switch
- FDA reiterated that it believed Alupent® to be safe for OTC use, but switched the drug back to Rx status

WELLPOINT

OTC Status of Second Generation Antihistamines is in the Public Interest

- The products meet all requirements for OTC statu:
- Long history of OTC marketing around the world
- Drugs are effective and safe
  - Lower incidence of side effects than existing OTC antihistamine products
- Switching the products to OTC status will make safer products accessible to the public

WELLPOINT

Example: Draft Labeling - Loratadine OTC

INDICATIONS: For the temporary relief of sneezing, itchy, watery eyes, itching of the nose or throat and runny nose due to hay fever or other upper respiratory allergies.

DIRECTIONS: ADULTS AND CHILDREN 6 YEARS AND OVER
One tablet once daily. Do not exceed recommended dosage. Prolonged usage should only be on the advice of a physician.

WARNINGS: If you are pregnant or nursing a baby seek the advice of a health care professional before using this product. **KEEP THIS AND ALL OTHER DRUGS OUT OF THE REACH OF CHILDREN.** In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

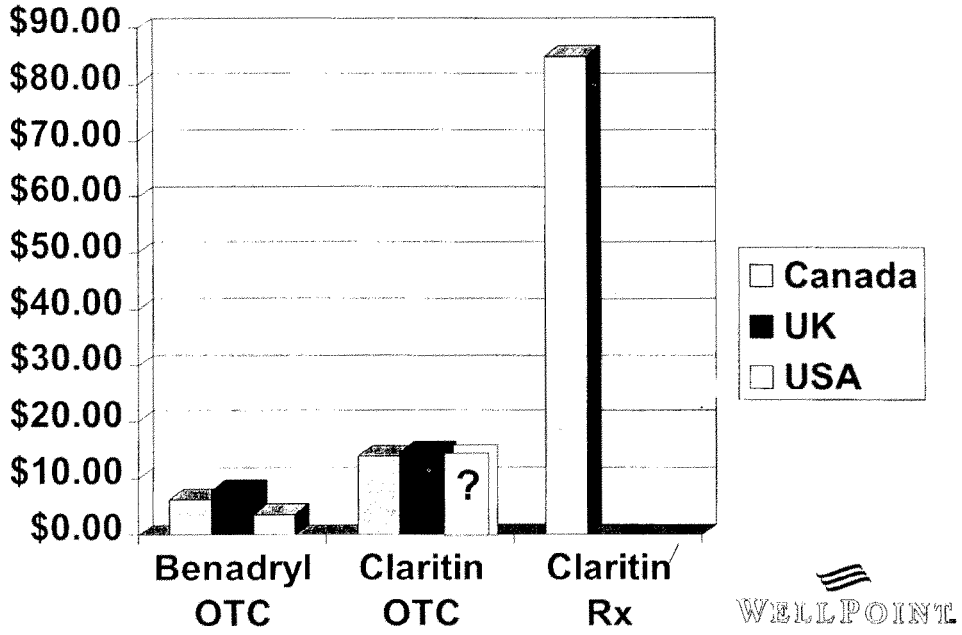
WELLPOINT

WellPoint's Request for the Advisory Committee, FDA and the Industry

- Advisory Committee
  - Vote today to recommend OTC status
- FDA
  - Act swiftly to switch the products to OTC status
- Industry
  - Work with the Agency to make these safe and effective second generation antihistamines readily available to the U.S. public

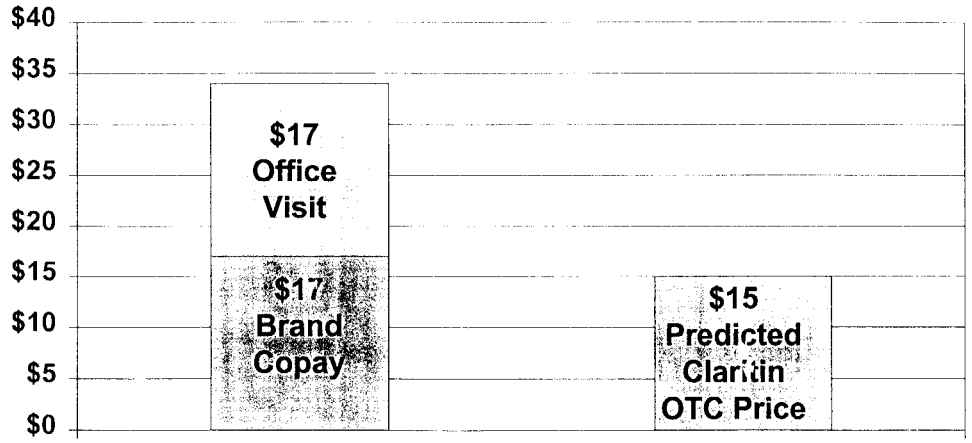
WELLPOINT

Potential OTC Claritin Pricing



WELLPOINT

OTC Cost Savings



WELLPOINT

Mr. BILIRAKIS. I am told that Mr. Kingham is the next witness.

I do want to apologize to all of you for not being here, but I really couldn't help it.

Please proceed, sir.

STATEMENT OF RICHARD F. KINGHAM

Mr. KINGHAM. Mr. Chairman and members of the subcommittee, my name is Richard Kingham, I'm a partner in the law firm of Covington & Burling in Washington, D.C. specializing in matters of food and drug regulatory law. I've been practicing in that field for nearly 30 years and have served in committees of the National Academy of Sciences, the National Institutes of Health, the World Health Organization and taught food and drug law in universities in the United States and the United Kingdom. And perhaps most relevant, I was counsel to one of the parties in what I believe remains the only judicial challenge to an Rx OTC switch in at least my memory.

I appear today on my own behalf, but I do of course represent pharmaceutical manufacturers in my day-to-day practice.

I thank you for the opportunity to appear and request that my written statement be entered into the record.

I start with the premise that as a matter of public health policy consumers should have access to safe and effective medicines that can be appropriately used and labeled for self-care. At the same time, it is absolutely critical that any switch of a product from prescription to OTC status be supported by adequate data demonstrating that the products can be used safely and effectively by consumers without a physician's supervision.

The manufacturer of the drug is in the best position to provide this data and the manufacturer's active involvement in a switch is crucial. Recent proposals to impose a switch without the manufacturer's support reflect, in my view, poor public policy and raise serious legal issues. I oppose those proposals which I believe would depart from 50 years of precedent concerning OTC switches since the enactment of the Durham-Humphrey Amendments in 1951.

First, I believe that collaboration between the drug manufacturer and the FDA is key to any switch. In evaluating a switch candidate, the FDA requires evidence to show that the drug is intended to treat a condition that can be self-diagnosed and self treated, that the drug will be safe and effective as used in an OTC setting, and that there is a safety margin based on prior prescription marketing experience. It is also critical to show that OTC labeling will be understood by consumers and provide adequate warnings and instructions so that consumers will not diagnose and self-medicate if they experience symptoms that should be evaluated by a physician.

A manufacturer's knowledge of all facets of a drug is indispensable to assessment of whether a drug meets the standards for a switch. The manufacturer has undertaken and maintains the full clinical development data concerning the drug and the manufacturer's in the best position to perform the new studies that are ordinarily required to support switch from prescription to nonprescription status. There are significant issues that can arise when drugs

are switched and testing is ordinarily required to look into those issues. The manufacturer is the one that carries out those studies.

Simple comparisons of a switch candidate to existing OTC drugs cannot substitute for genuine study of the drug's safety and effectiveness under OTC conditions of use and they don't meet the legal standards for a switch. Current law clearly provides that drugs must be evaluated on their individual merits and does not permit comparative assessments of safety or effectiveness. This makes good sense because attempts to rely on comparative evaluation of different compounds are prone to error.

Next, switching a drug over the manufacturer's suggestions would in my view implicate the manufacturer's established legal rights under the Federal Food, Drug and Cosmetic Act, under mantel precepts of administrative law and the United States Constitution.

A forced OTC switch would fundamentally change the terms of the manufacturer's approved license for the prescription drug and upset the settled expectations that the manufacturer had when it invested in development of the drug. Any compelled switch would also necessarily rely without the manufacturer's consent on proprietary data developed by the manufacturer. These actions would trigger core due process and property rights issues for the manufacturer and would, at a minimum, require that the manufacturer be afforded a hearing and potentially just compensation.

Finally, mandated switches would constitute unprecedented governmental interference in the drug development and marketing decisions of private firms. Since the passage of the Durham-Humphrey Amendments in 1951 FDA has never switched a prescription product to over-the-counter status over the active objection of the manufacturer. In the one prominent instance in which the FDA effectuated a switch without fully consulting all interested parties including the manufacturer and gaining the support of the manufacturers, the agency ultimately had to rescind that decision and the Commissioner of Food and Drug had to appear in a subcommittee of this committee to explain the action that the agency had taken.

Departure from the agency's otherwise settled precedent could seriously disrupt the drug development process. Firms carefully establish research plans and development strategies for a product's life cycle. These plans would be jeopardized by unanticipated switches triggered by a third party. To allow such a practice would create uncertainty and unnecessarily complicate the already highly risky business of drug development. New research and development could be chilled as a result.

I'll be happy to answer any questions.

[The prepared statement of Richard F. Kingham follows:]

PREPARED STATEMENT OF RICHARD F. KINGHAM, COVINGTON & BURLING

Mr. Chairman and Members of the Subcommittee:

My name is Richard F. Kingham. I am a partner at the law firm of Covington & Burling in Washington, D.C., specializing in matters of food and drug law and regulation. I have been practicing in the field for nearly 30 years, and have served on committees of the National Institutes of Health, the Institute of Medicine of the National Academy of Sciences, and the World Health Organization. I have lectured on pharmaceutical regulation at universities in the United States and the United Kingdom. Although I represent both prescription and nonprescription drug researchers and manufacturers, I appear today on my own behalf. I thank the Subcommittee

for the opportunity to present my views on the switching of drugs from prescription to over-the-counter status.

I start with the premise that, as a matter of basic public health policy, consumers should have access to safe and effective medicines that can be appropriately used and labeled for self-care. At the same time, it is absolutely critical that any switch of a product from prescription to OTC status be supported by adequate data demonstrating that the products can be used safely and effectively by consumers without a physician's supervision. The manufacturer of a drug is in the best position to provide those data, and the manufacturer's active involvement in a switch is crucial. Recent proposals to impose a switch without the manufacturer's support reflect poor public health policy and raise serious legal issues. I therefore strongly oppose these proposals, which would depart from the 50 years of precedent governing OTC switches since enactment of the 1951 Durham-Humphrey Amendments to the Federal Food, Drug, and Cosmetic Act.

Historical Development of FDA's Approach to Rx-OTC Switches

Historically, FDA has used three mechanisms for switching drugs. First, following enactment of the Durhman-Humphrey Amendments in 1951, FDA switched a number of drugs to OTC status using a rulemaking approach referred to as the "switch regulation," which was authorized under section 503(b)(3) of the Federal Food, Drug, and Cosmetic Act. This rulemaking process made sense in the 1950s and 1960s as a way for the agency to gain control over a variety of drugs that were marketed by different companies under different conditions, some Rx and some OTC, some with new drug applications (NDAs) and others without. The very same drug, with identical dosage and indications, might have been sold Rx by one company and OTC by another. Of course, that situation does not exist today, and FDA has not used this process to switch a drug for some 30 years (the last time being in 1971).

Second, beginning in the early 1970s, FDA relied on the "OTC Drug Review" as the principal vehicle for switching drugs to OTC status. This, too, made a great deal of sense for its time, since it was part of the agency's comprehensive review of the safety, effectiveness, and labeling of OTC drugs following the landmark 1962 amendments to the Federal Food, Drug, and Cosmetic Act. FDA switched approximately 32 drugs through the OTC Drug Review in the 1970s and 1980s. However, the OTC Drug Review has largely run its course, and it is not the focus of switch activity today.

FDA entered the third, and current, switch era in the mid-1980s when it began switching drugs through the NDA process. With very few exceptions, every switch today is accomplished through approval of an NDA or NDA supplement. This is suited to today's environment. FDA comprehensively regulates new drugs, both Rx and OTC, through the NDA process. The NDA process gives the agency the maximum degree of authority over all aspects of a drug, and provides the means by which manufacturers may invest in the development of proprietary data for submission to FDA in support of approval.

Collaboration Between the Drug Manufacturer and the Food and Drug Administration is Key to a Switch.

In evaluating a switch candidate, FDA requires evidence to show that the drug is intended to treat a condition that can be self-diagnosed and self-treated, that the drug will be safe and effective as used in an OTC setting, and that there is a safety margin based on prior prescription marketing experience. It is also critical to show that OTC labeling will be understood by consumers and provide adequate warnings and safety information, so that consumers do not self-diagnose and self-medicate if they experience symptoms that should be evaluated by a physician. These standards are vital to the continued integrity of the nonprescription market.

For the past decade, the switch of a prescription product to OTC status has in nearly all cases been initiated by the holder of an approved NDA, or with its approval, through the submission of a new application or a supplement with extensive data to support safe and effective OTC use and appropriate OTC labeling for the specific drug. This makes public health sense. The company that developed the drug in the first place and obtained the approval for the prescription drug knows the most about the drug.

Evaluation of a switch is necessarily conducted product by product, based on the specific data and merits of each product. Extensive prescription use is essential to the full characterization of a drug's clinical profile, and is thus is a prerequisite for OTC consideration. New information is often learned through commercial use that cannot be identified based on the limited number of patients involved in the clinical trials conducted for initial product approval. Sponsors seeking OTC switches are routinely required to provide a large body of safety experience reflecting both clin-

ical trial and actual use, as well as updated scientific information developed since the time of initial NDA approval providing an enhanced understanding of the underlying disease, current medical practice, and the pharmacology of the drug.

A manufacturer's knowledge of all facets of a drug is indispensable to assessment of whether a drug meets the standards for a switch. The manufacturer has undertaken and maintains the full clinical development of the prescription drug, and is in the best position to understand the existing clinical and post-marketing surveillance data, evaluate a drug's current safety profile, and determine if an appropriate safety margin would support use without a physician's care.

The manufacturer is also in the best position to perform the new studies that are typically essential to ensuring that a drug will be safe as used in an OTC setting, and that labeling can effectively communicate information to consumers about warnings and precautions. Significant issues can arise under OTC use that do not exist, or are of considerably less concern, when a drug is used in accordance with a physician's prescription and supervision. For example, use of a drug may cause interactions with other drugs that a physician could identify and manage, if closely monitoring a patient. These risks need to be carefully scrutinized, and data collected to ensure that consumers will properly comprehend product labeling and will not self-diagnose and self-medicate if they experience symptoms that should trigger a physician consultation. Actual use and labeling comprehension studies can address these questions. A switch should generally not be permitted unless considerable data are developed in addition to the data already present in the NDA for prescription use. The drug manufacturer is best situated to design, fund, perform, analyze, and submit the needed studies.

Simple Comparisons of a Switch Candidate to Existing OTC Drugs Cannot Substitute for Genuine Study of the Drug's Safety and Effectiveness Under OTC Conditions, and Do Not Meet the Legal Standards for a Switch.

Current law clearly provides that drugs must be evaluated on their individual merits, and does not permit comparative assessments of safety or effectiveness. This makes good sense, as attempts to rely on a comparative evaluation of different compounds are prone to error. Either data exist to support OTC use of a drug or they do not, and considerations of relative safety or effectiveness are not germane.

No more permissive standard may be applied to allow third parties without adequate data to initiate a switch based on purported product comparisons. To do so could put the public at risk. It would also constitute arbitrary and capricious action for the FDA to apply one standard to a manufacturer-initiated switch and another to a third-party switch. *See, e.g., Independent Petroleum Ass'n v. Babbitt,* 92 F.3d 1248, 1258 (D.C. Cir. 1996); *Airmark Corp. v. FAA,* 758 F.2d 685, 691-92 (D.C. Cir. 1985); *United States v. Diapulse Corp.,* 748 F.2d 56 (2d Cir. 1984).

Switching a Drug Over the Manufacturer's Objections Would Implicate the Manufacturer's Established Legal Rights under the Federal Food, Drug, and Cosmetic Act, Fundamental Precepts of Administrative Law, and the United States Constitution.

A forced OTC switch would fundamentally change the terms of the manufacturer's approved license for the prescription drug, and upset the settled expectations that the manufacturer had when it invested in development of the drug. Any compelled switch would also necessarily rely without the manufacturer's consent on proprietary data developed the manufacturer. These actions would trigger core due process and property rights of the manufacturer, and would, at a minimum, require that the manufacturer be afforded a hearing and potentially just compensation.

Section 505(e) of the Federal Food, Drug, and Cosmetic Act specifically requires that FDA provide notice and a hearing in order to seek basic changes to an approved application. Section 505(e) provides important due process protections for the holders of approved NDAs, and is a central part of the current regulatory scheme.

These statutory protections are directly reinforced by the due process clause of the Constitution and longstanding principles of administrative law, which hold that an administrative agency must provide an individualized hearing before taking specific action to modify or withdraw an approved license. The due process rights of licenseholders are recognized in a long line of judicial decisions tracing back to the seminal Supreme Court case of *Bi-Metallic Inv. Co. v. State Bd. of Education,* 239 U.S. 441 (1915), and its progeny. These due process protections are a fundamental safeguard against arbitrary and unreasonable agency action, and must be preserved.

In addition to raising due process concerns, almost any switch would also have to rely in part on data contained in the original NDA for the prescription drug to support OTC use. The company has proprietary rights in its NDA data, which could not be used without its consent, regardless of the regulatory procedures followed.

Companies make substantial investments to generate the data that are contained in an NDA, and such non-public commercial information is protected from disclosure by federal statutes such as the Freedom of Information Act and the Trade Secrets Act. The unauthorized appropriation of proprietary data would also implicate the Takings Clause of the Constitution. This is particularly true because a company would be deprived of the benefits of a prior investment of millions of dollars in the research and development of a new drug with no prior notice that it might be compelled to convert the product from prescription to nonprescription use.

Mandated Switches Would Constitute Unprecedented Governmental Interference in the Drug Development and Marketing Decisions of Private Firms.

Since the passage of the Durham-Humphrey Amendments in 1951, FDA has never switched a prescription product to over-the-counter status over the active objection of a manufacturer. In one prominent instance in which FDA effectuated a switch without the manufacturer's support (involving the bronchodilator metaproterenol), the agency had to rescind its decision.[1] This episode provides a cautionary tale for subsequent switches.

Further departures from the agency's settled precedent could seriously disrupt the drug development process. As indicated above, firms carefully establish research plans and development strategies for a product's life cycle. These plans would be jeopardized by unanticipated switches triggered by a third party. To allow such a practice would create uncertainty and unnecessarily complicate the already highly risky business of drug development. As it is, the Pharmaceutical Research and Manufacturers of America reports that only one in 5,000-10,000 compounds synthesized in the laboratory ever makes it to market, over 12-15 years at an average cost of $500 million. Adding greater uncertainty to the drug development process could chill new research and investment.

Once the Door is Open for Insurers and Other Third Parties to Initiate Switches, it Will be Difficult to Establish Appropriate Limits.

Insurers have significant incentives to compel OTC switches, because a switch effectively shifts drug costs from the health plan to consumers. If current law and practice are changed to permit insurers and other third parties to seek switches, there could be an outpouring of requests. It would then be difficult, if not impossible, for FDA to control the process and decide who should and should not be permitted to seek a switch. I strongly caution against any changes in law or policy that would produce such a result.

This concludes my written testimony. I would be pleased to answer any questions or to supply any additional materials requested by Members or Subcommittee staff on these or any other issues.

Mr. BILIRAKIS. Thank you very much, Mr. Kingham.

I think it's of note that Dr. Woodcock has chosen to remain in the hearing room to listen to all of this testimony. That is a very positive thing, and I want you to know, Doctor, that we appreciate it.

Mr. BROWN. Mr. Chairman, Dr. Woodcock, the chairman has asked people to do this for 5 years and finally someone did it. So, thank you. You made him so happy when you walked back into the room.

Mr. BILIRAKIS. Ordinarily I have to sort of recommend that they do it. Thank you very much, Doctor.

The Chair recognizes Mr. Greenwood for him to inquire.

Mr. GREENWOOD. Probably Ms. Woodcock was going to sit here for another 5 or 10 minutes, and now she's stuck for the rest of the afternoon.

Mr. Downey, I believe you said that your company filed two patent challenges to Prozac, is that your testimony?

Mr. DOWNEY. It was a single patent challenge, but it challenged two different patents.

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[1] *See* 48 Fed. Reg. 24926 (June 3, 1983).

Mr. GREENWOOD. Could you specify—and you lost the first one and won the second one, is that correct?

Mr. DOWNEY. Correct.

Mr. GREENWOOD. Could you specify exactly what was at issue in this cases?

Mr. DOWNEY. Yes. In the patent that expired in 2001, in February of this past year, the principle issue is whether the best mode for making the product and practicing invention was disclosed in the patent, which is one of the legal obligations of the patent applicant. The courts ultimately concluded that the best mode was disclosed or the disclosure was adequate and the patent was sustained.

The second patent was the one that expired, and it would expire in 2003, and we challenged that patent on the grounds that it was not sufficiently different from this patent expiring in 2001 to be independently patentable. And that, generally, was the idea of one invention/one patent. If you get a second invention—a second patent for the same invention, that runs afoul of the rule of double patenting—against double patenting. And that was the grounds in which the Court of Appeals for the Federal Circuit in an en banc decision—well, in a panel decision directed by the en banc panel struck down that patent just a week or so ago.

Mr. GREENWOOD. Now, in your testimony you also said that you thought that at the time when a patent is asserted, you noted that there was not an adversarial situation, that there was no one to argue at that time against the patent. Are you actually arguing that there ought to be and that that would be the case for all patents?

Mr. DOWNEY. No. I'm suggesting that that is—I'm not making that suggestion. What I'm saying is the system we have is the product of that process, and that process had led in my judgment to a number of unpatentable ideas obtaining patents which once they're obtained, are entitled to presumption of validity. That is the basic problem we confront in getting our products to market.

I'm not suggesting that it's a—that the solution to that is to create the patent application as an adversarial process——

Mr. GREENWOOD. Well, are you suggesting that there is a solution to that?

Mr. DOWNEY. I think the best solution is one that's in the current law and one that's carried over into the Brown-Emerson Bill, and that is to ensure that there's incentive once the patent has been granted to challenge that patent if it's weak or challengeable. In the case of the Waxman-Hatch Act and the Brown-Emerson legislation that incentive is the 180 days of exclusivity for the successful patent challenger.

I also think the Brown-Emerson Bill improves current law by providing that if the first challenger settles the case, subsequently the exclusivity for a successful challenger then rotates to the second in the line. So, I think that's a significant improvement. I also think that's an improvement that will eliminate the 30 month stay, which is another problem.

In the normal patent case if it's a chemical compound or electronics patent and you're challenging the patent, normally you'd be going to market and the patent holder would have to obtain an in-

junction to stop you from marketing. If they get that injunction, they have to post a bond. And if the patent challenger ultimately wins the case, they recover their lost profits.

In the case of the automatic 30 month stay, there is no bond. In essence, that gives the patent holder and the pharmaceutical industry a free preliminary injunction with no downside risk. And I think that's an area where the current law also needs to be changed so if there is a challenge during the case of Prozac and we're kept off the market by a patent ultimately declared invalid, we would recover our loss profits for that period that we're kept off the market. I think that's an improvement that needs to be made in the current legislation. But those are some of the problems that I see.

Mr. GREENWOOD. Does the generic industry support user fees to help speed products to market the way——

Mr. DOWNEY. As an industry we do not, and I think I can add why. In the case of the Office of Generic Drugs has approximately 125 people. I think with as few 150 or 175 you could have products actually approved in the 6 months. And I personally believe, and I think our industry believes, that a user fee program for 50 full time equivalents is not—is the wrong response to a fairly small problem. I think that simply a line item appropriation that would maintain the Office of Generic Drugs in an appropriate level to process the applications in a timely basis is the right approach. And I would say in response to some Dr. Woodcock's testimony, many firms have a much shorter than 18 month approval cycle. I know that in our case it's more like 12 or 15 months. I know your constituent Teva would also have something in the neighborhood of 12 or 15 months. And usually the period over a year has to do with characteristics of the product.

For example, the United States Pharmacopeia establishes standards for most products. And if a product is in the Pharmacopeia, you get a much shorter approval time. But I can tell you if it's not and we submit an application, we get extensive chemistry comments because those specifications haven't been worked out in advance. So there's some other factors that figure into the approval process and really a small increment—the Office of Generic Drugs I believe could really bring the process down to 6 months.

Mr. GREENWOOD. Thank you.

Mr. BILIRAKIS. Mr. Brown to inquire.

Mr. BROWN. Thank you, Mr. Chairman.

I don't know where to start. Dr. G;over on behalf of PhRMA says we shouldn't attempt to improve upon Waxman-Hatch Act because any changes would jeopardize research and development. Yet, PhRMA member companies enjoy—PhRMA member companies, first of all, charge U.S. consumer often times two and three and four times what consumer and other wealthy developed industrial democracies are charged. PhRMA companies have been the most profitable businesses industry in the U.S. for 20 years running, whether it's return on investment, return on equity, return on sales. PhRMA companies have enjoyed the lowest tax rate of any industry in America because of the research they do, something I in fact support. PhRMA companies have spent more money in marketing than they have research and development. And also govern-

ment and foundations taxpayers through NIH foundations, other government agencies spend half—do half of the research and development in dollar terms have of the research and development in this country on prescription drugs.

And then PhRMA tells Congress, Dr. Glover has told Congress and told the American people in very expensive ad campaigns that anything Congress does that might effect prices will curtail research and development.

Now, Dr. Glover in his testimony said "There's no need to amend Waxman-Hatch Act to deal with this issue, and settling cases, and he is encouraged by the courts it avoids the expenses of litigation and it can create results that accommodate the interests of both parties." While the corporate special interest flavor of this Congress and this Administration might suggest otherwise, our job in this institution is in fact to protect the public interest. You're a lawyer, you do a good job I'm sure for your client, that's why you're here. You're impressive. You've lad out a good case today. But how does it serve the public interest when, you know, one party, the generic is happy. The PhRMA company is happy. Yet prices don't come down when generics in the marketplace would in fact bring prices down. How does that compromise under Waxman-Hatch Act the way it works now, how does that serve the public interest?

Mr. GLOVER. In the pharmaceutical industry there are two ways in which the public interest can be served. The first is that we make sure that we have a system in place that will allow for innovation for the current population as well as innovation that will prevent future generations from suffering from the same diseases that we currently suffer from.

The other, which we tend to focus on in these debates, is that the generic industry by virtue of providing drugs at lower costs is another way to provide protection to the public health.

Now, in a circumstance where there is a patent settlement, in some cases it will result in the innovator's patent being protected. That, by itself, does not mean that the public interest is not being served. It is in our interest and the interest of the system that we've designed that the patents are sometimes protected. In other cases, as Mr. Downey described in his testimony, the generic interest gets to the market prior to the expiration of the patent that would have otherwise kept it off the market. And in one of the cases that he described, the subsequent challenges to the patent did not get on the market because they lost their patent infringement cases. So in those circumstances, both of them are circumstances in which the public was better off by having the parties settle the case than it would have been to expend further sums and more time in litigation to the end.

Mr. BROWN. But in case after case this settlement between two parties, both of whom can profit immensely from those settlements, keeps a less expensive identical drug from going to the market giving consumers choice and giving consumer lower prices?

Mr. GLOVER. It is not true that simply by having lower cost you give consumers choice. You give consumers choice today, you take away choice tomorrow.

And with respect to this being case after case, please bear in mind that there are only three cases in which there have been sup-

posedly any complaints by the FTC regarding settlements between pioneers and generics. It is simply not the case that this is a common place occurrence that the FTC has deemed to be anti-competitive.

Mr. BROWN. Well, if it's three cases, then it's cases where as we see this happening more and more, and it's obviously going to happen more tomorrow than it did yesterday, that's clearly the trend——

Mr. GLOVER. I actually think that's unlikely given that we now see the FTC's interest in these matters and we now have some clarification with respect to the way the courts are going to interpret the 180 day exclusivity, I think it is unlikely that you're going to see more and more of the settlements between pioneers and generics. In fact, that is a downside of the ambiguity of the scrutiny that is coming out of the FTC is that it will make the system substantially less efficient because you cannot have efficient settlements where they're appropriate.

Mr. BROWN. Well, I would argue it won't be less likely or PhRMA wouldn't be putting the kind of resources into opposition of this bill.

But let me make one other point with Dr. Delgado. It's not really—it's a simple question. My understanding there are 11 members of the National Alliance for Hispanic Health and the corporate advisory council, six of those, if I could name them quickly, Karen Katen whose with Pfizer, Karen Dawes whose with Bayer, David Anstice is with Merek, Aldrage Cooper is with Johnson & Johnson, Gino Santine with Eli Lilly, Kevin Reilly with Wyeth. Is that correct what I just said, those 6 out of the 11 and those people are actually under——

Ms. DELGADO. Yes, they are on our corporate council. They contribute less than .25 percent of our budget, and we are a health organization that does not accept money from tobacco or alcohol companies. We work with people who try to save lives, yes.

Mr. BROWN. Thank you.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Bryant to inquire.

Mr. BRYANT. I thank you, Dr. Delgado. Let me just ask you one question I had intended to——

Mr. BILIRAKIS. You might lift that mike up closer to you.

Mr. BRYANT. Oh, okay. Let me slide closer here.

Based on your testimony and the statistics that I think have been recited several times today by panelists, would you care to characterize the direct to consumer advertising that is being done in this area as successful in terms of reaching people who would otherwise be untreated?

Ms. DELGADO. Yes. I think it gets people to think about their illness. And not just in the sense of having them go in for care, but also thinking about maybe I should take my medicines or things like that.

Mr. BRYANT. Let's see, I wanted to ask Dr. Glover a question also. I have a short period of time here, and I don't find it right now.

But in essence my understand is that on average the drug companies spend something like $500 million in developing a drug. I don't know if that's—is that ball park?

Mr. GLOVER. That's correct. That's an estimate, yes.

Mr. BRYANT. And do you know, and I know Mr. Downey next to you may well know this perhaps better than you, what the cost would be that would be associated with bringing a generic to market on average? A generic drug?

Mr. GLOVER. I will pass to Bruce, but our expectation is that it is a fraction less than 1 percent of the cost to bring the pioneer to market.

Mr. BRYANT. And what is your source representing the pharmacy side of recovering those R&D costs?

Mr. GLOVER. We need to recover the R&D costs by virtue of marketing our drug and the income that we receive from marketing our drugs. And as the economics will show that of the drugs that are approved by FDA only a small fraction of those drugs generate enough income to cover the average $500 million cost for those drugs. And as a result, just virtue of the economics, it is necessary that a certain percentage of all drugs approved must be drugs that far exceed the $500 million cost in order to make up for the cost of the other drugs.

The additional thing that we have to keep in mind that we're doing with the income from the drugs that are being sold, is that we're not merely recovering the R&D for drugs that have already been developed, but we're also trying to have enough money to fund the R&D for the next generation of cures which are likely to be more complex, more expensive and take a longer time to get to approval.

Mr. BRYANT. In your R&D do you have drugs that strike out, that fail, that don't work?

Mr. GLOVER. Absolutely. In the drug development process, failure occurs everywhere in the process. It occurs starting with animal studies, starting with first generation, second generation animal studies, first trials into humans. You may find toxicity in certain populations that you didn't find in other populations.

Mr. BRYANT. Let me ask you this, and again I want to jump down to Mr. Kingham and then go back and let Mr. Downey talk.

To your knowledge do the generics have strike outs and failures? They have a better batting average than you do, don't they?

Mr. GLOVER. They have a substantially better batting average in the sense that they are relying on us having found the magic bullet amongst many that are not magic bullets. So they are simply faced with the task of making a copy of what we have determined to be the effective drug.

Mr. BRYANT. Okay. Mr. Kingham, let me ask you very quickly, in terms of section 503(b)(3) of the FDA are you aware of any instance of this Act, are you aware of any instance where the FDA itself moved a prescription drug, converted it over to a OTC drug over the objection of the manufacturer of that drug?

Mr. KINGHAM. No, I'm not. I'd also point out that that provision has not been used for 30 years. The last time it was invoked was in 1971 for a drug called Tolnaftade. It's essentially been superseded by other legislation.

Mr. BRYANT. Well, would forcing a switch to this former Rx over to an over-the-counter drug over the objection of a manufacturer, would it result in the consumers being forced to pay more out of pocket expenses for the drugs that they use? In my case, I use one of those, would I have to start paying for it myself if my insurance company didn't pay for it?

Mr. KINGHAM. I would assume that for those people who have drug benefits under their insurance policies that don't cover OTCs, that would presumably be the result.

Mr. BRYANT. And to be sold OTC a drug must be safe, a consumer must be able to self-diagnose what the problem is and the label itself on the container must be comprehensible to the consumers. If the FDA is allowed to do these switches over the objection of manufacturers, who would perform these label comprehensive studies?

Mr. KINGHAM. Well, I don't know of anybody but the manufacturers who do them, and usually in addition to label comprehension studies, some actual clinical trials are required as well. And the only people who do those in our system are the manufacturers.

Mr. BRYANT. Do you think this forced switch might impact on the ability of pharmaceutical companies to innovate?

Mr. KINGHAM. It could affect, it's one of a number of factors that effect investment decisions that companies make, yes.

Mr. BRYANT. All right.

Mr. Chairman, if I might ask for a unanimous consent to have perhaps an additional minute?

Mr. BILIRAKIS. Without objection. I hear no objection.

Mr. BRYANT. Mr. Downey, if we could go back to you now, I wanted you to get the last word in in terms of responding to Dr. Glover on those numbers and statistics I mentioned.

Mr. DOWNEY. Well, it's highly variable the amount of investment required to bring a generic product to market. In the least expensive case, $1 million, $2 million for a very simple product. In other case we've spent at Barr $30 to $40 million to attempt to bring a generic Premarin to market, and we still haven't done it. And that's for a variety of reasons, mostly regulatory. So there's no set answer to that question.

I will point out, and I'd be happy to document this in supplementing my testimony, R&D is a percentage of gross profit. Our company spends more than Merck or Johnson & Johnson or I believe any of the innovative companies. They always say the percentage of investment in R&D versus sales, well their margins are almost 95 percent, so sales and gross profit are the same. In our case gross margins are much lower percentage basis.

So if you look at the gross profit as disposable income for a company, Barr and many of our competitors in our generic industry spends a higher percentage of our gross profit on R&D than the innovator company. So I think we really are a research-based firm, and frankly we spend a much lower percentage of our gross profit on sales and marketing costs. Much, much lower.

Mr. BRYANT. Thank you.

Mr. BILIRAKIS. Mr. Pallone to inquire.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask Mr. Downey a couple of questions.

If I listen Mr. Glover's testimony where he talks about how there are few patent disputes. You know, he says despite the generic industry's arguments to the contrary, data show generic applications have not raised or encountered any patent issues that have delayed their approval, and he gave us some facts in that regard. But then Mr. Downey, you go on to talk about the stagnation of the growth of generic substitution. Nearly two decades after Waxman-Hatch Act, generic substitution rates, however, in the low 40's area. You talk about how this National Institute for Health Care Management foundation study showed that they through legislation and exploitation of legal and regulatory loopholes, the brand names have extended the anticipated market exclusivity from 12 to 18 years. An accumulative effect has resulted in extending product monopolies by almost 50 percent.

I mean, I know you're mainly talking about price and you know to the extent that price is an issue here. But how do you explain the two? I mean, it's almost like opposites?

Mr. DOWNEY. Well, I think in my testimony I indicated BusPar. BusPar is a product recently where generics were kept off the market by a late listed patent.

I think a recent example of Nicorette gun which was kept off the market by—sort of a nightmarish system of regulatory questions about the labeling and the patient materials. I think there are a number of instances where products have been kept off the market, either through regulatory manipulation or through patent manipulation. And I think both are important and I think Congressman Brown's bill addresses both. You have questions about bio-equivalence, which would be modified in the new legislation. You'd have questions about citizen's petitions tightened up in the new legislation. You would eliminate the 30 month stay so if people really did want to market at risk that had the ability to do it. So, I think there are a number of things that can be done and are in the Brown-Emerson Bill that would clear these pathways to bring our products to market.

But I think the fundamental thing, the biggest single incentive to work to bring these products to market is the 180 days of exclusivity to challenge patents. And without that, you're going to have a long, long delay in market entry.

Mr. PALLONE. We didn't have much mention today about the citizen petition process.

Mr. DOWNEY. Yes.

Mr. PALLONE. You just mentioned that. Do you want to tell us a little bit about that, because again that's addressed in the Brown bill, you know, the effort to—I guess under the GAAP you have to require to certify that petitions are factually based, that they can't be used for any competitive purposes, otherwise they'd be investigated by the FTC. I mean, tell us how this process is used and how we can improve it?

Mr. DOWNEY. I'll give you a real life example. Our company brought to market a generic version of Coumadin, warfarin sodium, been off patent for 40 years. As our application neared approval and was within, in my judgment, 30 days of approval the innovator firm filed a citizen's petition in which they recited almost comically in the first page that they learned the previous day that a generic

product was about to be approved and they were filing this 50 page petition saying why approval of that product would be imprudent. So if you read it literally, they prepared this document within—this 50 page document overnight to file with the FDA.

I believe that petition—as a practical matter, I believe the FDA chooses for reasons they think are sufficient to not approve the products until they can resolve the citizen's petition issues. And if you time your citizen's petition correctly, as in the case that I just described, working through the petition, preparing a response takes months and results in months of delay.

Mr. PALLONE. But how do we improve on that? I see what we're proposing in the Brown bill. How would it improve on it?

Mr. DOWNEY. Well, I think the Brown bill would have attached some consequences if you filed a petition that was ultimately denied. I think, frankly, it's a very difficult problem because people do have First Amendment rights and you don't want to stop people from making legitimate safety petitions to the FDA.

I personally believe the best way to do it is decouple the two processes. And that is if you have a product in the market and you have established approval processes for the generic product, let it go forward. And then if there's a problem, that will manifest it later.

If you as an innovator think there's a problem with a generic product being approved, you have years in advance of the application to make that known to the FDA. Only in an emergency, an unusual situation would something come up at the last minute that should delay the approval.

So, it's a difficult problem but I think the Brown-Emerson Bill addresses it in a sensible way.

Mr. PALLONE. Thank you.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. I thank the gentleman.

Ms. Delgado, I know your role here is to sort of support, if you will, the direct-to-consumer TV advertising, is that correct?

Ms. DELGADO. Well, my role here is to represent our membership, which are Hispanic consumers.

Mr. BILIRAKIS. I'm glad you said that. That being the case, let me shift over to you. You've sat in the audience, and I'm not sure whether you know if it's unfair of me to bring it up, please let me know, the OTC situation where the prescription drug might be shifted over to the over-the-counter.

Ms. DELGADO. I'm very familiar with that, yes.

Mr. BILIRAKIS. You are familiar with it. What is your organization's, on behalf of your people, what is your opinion on that?

Ms. DELGADO. I think that the FDA has a very important role that should not be pushed by people who are more concerned about the cost to themselves rather than consumers. I am concerned that the decision is driving more by pushing the costs off to consumers.

For example, we know some of the managed care companies encourage their members to take part in alternative health because they don't have to cover those costs. And I think that when you have an OTC, your consumer already has limited funds will cover more of those costs. So we're concerned about that.

We would like the FDA to proceed as they always did on good science and not to feel pushed in way or another.

Mr. BILIRAKIS. Well, I'm not sure how to interpret all that.

Ms. DELGADO. That means that when the big boys fight, that science should be the one who rules the day. And what's good for consumers, that—I mean medications need to be out for a while before we know that they're really as good, as effective as they are supposed to be. We in the United States are very different than in other countries, and I'm very concerned when they compare us to other place and say "Well, there we can get a drug out quicker and it's over-the-counter and you can get it."

Mr. BILIRAKIS. You heard me say, and nobody's disputed it, the insurance companies that cover drugs will cover prescription drugs.

Ms. DELGADO. Right.

Mr. BILIRAKIS. So if drugs shift to over-the-counter, I guess conceivably it probably would be less expensive to the consumer. But I'd say, whether it is or whether it isn't, the point of the matter is that it will probably not be covered by the insurance policy. Is that right?

Ms. DELGADO. Exactly. Exactly. And that we don't see as good.

Mr. BILIRAKIS. All right. That being the case, how do you feel about that?

Ms. DELGADO. Let me back up. I think one of the problems is when we look at health coverage in America from that hospital-based position system to more in-home and patient-driven, which means that in fact somehow the patient's going to have more medical home care costs. And our system doesn't do that. So we do this patchwork approach of solving it.

I don't think it's good to just making OTC and then make the consumer pay for it. Because even though the costs are low, those costs may still be higher than their co-pay, or whatever they may have to pay for that medicine. It's a very complicated issue and it's unfair that whenever the price of drugs go up, we oh, or there's more expenses on it. Because I'm happy people are spending less time in hospitals.

We work very much on HIV/AIDS. We're happy to see less time in hospitals, more part with medicine.

Mr. BILIRAKIS. Let me ask you then about the direct-to-consumer TV advertising. I don't know whether it was mentioned while I was gone, and Mr. Downey may have been alluding to it earlier, but in one of our prior hearings just a few days ago, we had a witness who put up a chart that indicated that direct-to-consumer TV advertising—at least that's the way I interrupted it and I've checked with some staff here and I think they kind of agree would amount to about $300 billion over 10 years. I know it seems out of the ordinary. And I am relating it to the $300 billion that's been allocated in the budget to prescription drug coverage for seniors.

So, regardless of whether this $300 billion is a correct figure or something considerably less than that, still we're talking about an awful lot of money.

Ms. DELGADO. But the other side is what's the cost of not getting care.

Mr. BILIRAKIS. Yes. But whether it be $300 billion or whether it be $2.5 billion times 10 years, or whatever the figure might be,

that's going to be a part of the price that your consumers will pay, will it not?

Ms. DELGADO. Yes.

Mr. BILIRAKIS. All right. And you still feel that the advantages of that advertising outweigh the advantages or the disadvantage of additional costs?

Ms. DELGADO. The advantages of advertising is having people going for care, and I want healthy people not people who are working that are ill or not able to work. So I think with——

Mr. BILIRAKIS. Are those same people paying more for their drugs because of that advertising?

Ms. DELGADO. I would assume that they probably are paying more, but they're also going in for care.

Mr. BILIRAKIS. Yes.

Ms. DELGADO. So I think it's a tradeoff. I mean, it's very difficult but people need to go in for care. And if it gets them in, that's the first step.

Mr. BILIRAKIS. Yes.

Mr. GEISER. Mr. Chairman?

Mr. BILIRAKIS. Yes, sir.

Mr. GEISER. We request permission to present two charts that have a bearing on this discussion.

Mr. BILIRAKIS. You want to put them into the record, is that what you're saying, sir?

Mr. GEISER. Yes. And to have Dr. Seidman speak to them for a moment?

Mr. BILIRAKIS. I don't know about that. But we are very glad to consider anything that you have to present for a matter of the record.

Mr. GEISER. Well, the two charts demonstrate and speak to the issue that was just discussed and present our best guess on what the impact of the OTC switch would be and compare what we project the price to be to——

Mr. BILIRAKIS. Mr. Geiser, your time was up, obviously, but if there's no objection and if there is objection—actually, at this point in time I'm going to have to call on Mr. Burr to inquire, because you haven't had your opportunity to inquire Mr. BURR. The Chair is correct.

Mr. BILIRAKIS. All right. We'll do that.

After Mr. Burr testifies if you make that request, and if there's no objection, I will allow the charts. But I think I will just allow you to explain them if you wanted to very, very briefly.

Mr. GEISER. Thank you.

Mr. BILIRAKIS. All right, Mr. Burr, please.

Mr. BURR. I thank the Chair and let me take this opportunity, Mr. Chairman, to point out to those that are left, even though I've been absent, Dr. Woodcock has stayed. This is probably one of the first times, whether it's the FDA or any other agency, that I've seen somebody who testified actually take the time to stay and listen to the other panels. And I want to commend her for it, because——

Mr. BILIRAKIS. I've already done that, Richard. I appreciate you concerning that.

Mr. BURR. I felt if I didn't do it, she would think that I had slacked off a little bit.

Let me also say to Dr. Delgado, it's refreshing to find somebody with the focus in the right place. Your answers are genuine and for the right reason; it's because your focus is on what's best for patients. And I think, hopefully, most would agree with you that the better educated consumers are in the market place, the easiest that we can make it for patients to access care, care a big umbrella. Hopefully the sooner they do it, the healthier they are. And I think we've lost focus up here of the fact that one of the impacts that we can have from a legislative standpoint is actually to prevent people from visiting the hospital for extended periods of time. Some of that is the pharmaceutical regiment, some of it's the technology that's in devices that we can now do in doctor's offices versus a hospital stay. And I think we lost track of that when we had a debate not long ago as it relates to severe cuts in home care, which was originally designed to keep people out of the hospital. And we're trying to make up for the mistakes that we make.

Let me ask each one of you: Is there anybody that disagrees that the FDA currently has the authority to make a determination that switches a drug from prescription to over-the-counter? Is there anybody that feels the authority does not exist at FDA today to make that determination?

Mr. KINGHAM. Representative Burr, if you mean over the objection of the manufacturer through the procedure that has been suggested that's I think one of the instigation for this issue to be discussed here today, yes, I think there are a couple of very serious problems that are presented by that.

Mr. BURR. I understand that in your testimony, I'm sorry I missed it but I have familiarized myself with it, that you don't feel that there should be a decision to move over-the-counter based upon the pharmaceutical company's objection. My question is technical though. Does the FDA have the authority to make that determination in your opinion?

Mr. KINGHAM. I think that in the procedure that is under discussion some very serious legal questions are raised by the proposed procedure that's intended to be used. The first has to do with whether due process would be accorded through the rulemaking procedure that is proposed in the context of the recent request. I don't think that it would be, and I don't think that provisions of the statute requiring a hearing would be satisfied as well.

Perhaps even more important because it's fundamental to the outcome is that the court decisions relating to FDA rulemakings have held that the agency when it engages in a rulemaking process that is based on science, must disclose the scientific basis, the full scientific basis for the decisions that it's making, otherwise its rulemaking can be set aside.

The problem here is that the key data or certainly some of the key data relating to a switch are proprietary data that are trade secret or confidential. They either belong to a drug manufacturer and cannot be disclosed on the record without a violation of the Trade Secrets Act, the Federal Food, Drug and Cosmetic Act and the agency's own regulation.

So it's a very difficult question in the situation that has been represented here. It's never arisen before. We've never had to deal with it because there's always been a collaborative process with the manufacturers and the FDA.

Mr. BURR. I certainly raised that question earlier with Dr. Woodcock, and I think she, with the advise of others from the FDA felt that there was a protection that they had to adhere to on trade secrets. I take from yours the protection of those trade secrets would preclude them from living up to all of the hurdles that they had to overcome?

Mr. KINGHAM. I believe that's right.

Mr. BURR. I'm sure that we'll get some additional legal interpretation from the FDA on their views, but I appreciate your personal views.

Yes, sir?

Mr. GOLENSKI. Mr. Burr, if you meant asking all of us the question, RxHealthValue gave a statement to the FDA expert panel regarding the safety issue of OTC transfer of the antihistamines on behalf of WellPoint, and we did that for two reasons. One was we felt that the only way these kinds of questions that you're essentially raising are going to be asked given the unprecedented nature of the request would be to actually do it. And we supported WellPoint's right, and in fact supported them aggressively to bring the question.

And second, a content issue and I think it's a question that your colleague Mr. Bryant asked earlier in the morning of Dr. Woodcock but I don't think was specifically addressed, and that is we were concerned that much of the safety data that you would need to have for an OTC switch in fact exhibits in the world and that unfortunately is not within the boundaries of the United States, but these medications specifically have been over-the-counter for years in Europe and we felt that the quality of the scientific work that was done in that part of the world was adequate and we felt it should be used, and we said that in our statement to the FDA panel.

Mr. BILIRAKIS. Would the gentleman yield briefly?

Mr. BURR. Be happy to yield.

Mr. BILIRAKIS. Even though his time has expired.

Mr. BURR. I don't think the Chair has started the clock.

Mr. BILIRAKIS. Mr. Kingham, what's the remedy? I asked this question of Dr. Woodcock. What is the remedy for the manufacturer in the case where a unilateral decision has been made to go OTC without the approval of the manufacturer?

Mr. KINGHAM. Well, it's very unclear because the system, despite what's been said, is not really set up with that in mind and it hasn't happened, so it isn't clear what would play out if in fact the FDA went forward and tried to compel a switch. It would be an unprecedented act.

There are a variety of possible ways in which the issue could be raised. It could be raised in the context that the change could not be made, except through a full evidentiary hearing process under section 505 of the Federal Food, Drug and Cosmetic Act. Another possibility is that a suit could be brought to challenge the regulation itself, either——

Mr. BILIRAKIS. Well, the suit is always available.

Mr. KINGHAM. That's right.

Mr. BILIRAKIS. I mean within the FDA itself.

Mr. KINGHAM. Within the FDA, of course, there's an administrative review process. There's an appellate process within the Center for Drugs which Dr. Woodcock mentioned in her testimony earlier, and one can go above that up to the Commissioner and that sort of thing.

But one question here is if there were simple notice and comment rulemaking of the type that some people are advocating, there wouldn't be a hearing in the usual sense of the word. There would be an exchange of paper, but no hearing in which people would be given an opportunity to confront the other side's evidence of witnesses in the way that we ordinarily understand.

Mr. BILIRAKIS. All right. I'm just going to take the purgative if I may. I'm sure Mr. Brown won't mind.

Dr. Glover, you're an M.D. You're also an attorney. J.D. and M.D.

Mr. GLOVER. Yes.

Mr. BILIRAKIS. You have heard the testimony of Dr. Woodcock earlier on the direct substitution the bio-equivalency, etcetera, of generic drugs. Do you agree?

Mr. GLOVER. There are——

Mr. BILIRAKIS. And I might add, Dr. Delgado made the comment before I came in, but as I understand it for certain ethnic groups they may not work. Maybe she was speculating? I don't know whether there's any——

Ms. DELGADO. No, I'm not speculating.

Mr. BILIRAKIS. No speculation. It's based on facts?

Ms. DELGADO. Yes.

Mr. BILIRAKIS. All right. Go ahead.

Mr. GLOVER. Mr. Chairman, I think that therefore there are two issues here. The difference in ethnic groups is something that we've known about for many, many years. We know, for example, that certain populations have a different degree of activity, the enzymes in their liver where many drugs are cleared, certain populations are more susceptible to the effects of certain drugs that act on certain receptors or vice versa and things of that nature. And as a result for certain drugs you will want to test that drug, whether it's pioneer or generic, in a particular population where it might be used and to make sure that it is effective or not toxic in each of those various populations. And we also see this played out on the international scene where in certain foreign countries, particularly Japan comes to mind, where many drugs that might be on the market here need to be separately tested on the Japanese population to make sure that there are no unusual metabolic properties of the Japanese population that may have a difference in the drug.

You then take that to the next issue, which is what is the impact of that or anything else on bio-equivalence for pharmaceutical products.

With respect to generics, Dr. Woodcock focused on the idea that generics were to be directly substitutable. We started, I believe her first comment was that they were identical and then got to a position with some questioning that there was indeed some variation

that would exist between the generic and the pioneer. And indeed as she testified, between pioneer products from batch-to-batch.

We believe, however, that the variation that FDA allows is substantially wide. That is, FDA permits a variation of as much as plus or minus 20 percent of the bio availability of the pioneer drugs——

Mr. BILIRAKIS. Is that enough of a safety factor to cover their concerns?

Mr. GLOVER. The plus or minus 20 percent is a very large factor in the view of the pioneer companies. Moreover, even to the extent that we could get comfortable with a 20 percent variation with respect to a generic, with respect to the pioneer, that then allows for a possible 40 percent differentiation between one generic versus another generic.

As you very well know if you have any experience in getting generic drug products filled at the pharmacy, you can go in 1 week and get generic drug A and the next week generic drug B by a different manufacturer, both generic to the same pioneer product. But with respect to each other they could be on either side of the variation. And so it's that degree of variability I believe is substantially troublesome and there are particular products in the marketplace where that kind of variation may very well cause a difference in a toxicity or certainly a difference in efficacy in the population.

Mr. BILIRAKIS. I didn't expect all of that.

Mr. BROWN. Mr. Chairman, since we begun a new debate here, I think it's only fair that's Mr. Downey——

Mr. BILIRAKIS. You're reading my mind. I had planned to do that, yes.

Mr. BROWN. Mr. Chairman, I've been——

Mr. BILIRAKIS. We don't always agree——

Mr. BROWN. I've sat next to you so long I can read your mind.

Mr. BILIRAKIS. I guess that's the case.

Mr. BROWN. I was just saving you the effort. Thank you.

Mr. DOWNEY. Well, we do agree with Dr. Woodcock and I would strongly disagree with Dr. Glover on this point. The whole structure of the FDA approval process is to have pioneer products proven safe and efficacious. And then the generic product to be proved same as the brand.

In the case of the approval process we have all sorts of requirements. We have to do the same chemical warranty, the same mode of administration, we have to prove that the active ingredients absorb the same rate and at the same extent as the brand product. And we do that in this context of the same standards that the brand products use to take the products they use in their clinical studies to the marketplace. They also do bio-equivalence studies to show what they're actually going to market is bio-equivalent to what they actually use in their chemical studies. So it's the same set of standards applying both to the brand industry providing that their products are the same as it is to us proving we're the same as the brand.

So, we agree 100 percent with Dr. Woodcock. And, in fact, I think her testimony forms the basis that we ought to mandate generic substitution in Federal programs and ought to support Congress-

man Pallone's bill to preempt all the State requirements that don't recognize these very rigorous standards imposed by the FDA.

Mr. BILIRAKIS. I had hoped that this hearing would be sort of the unanimity in terms of the efficacy of generics.

I'm going to have to cut it off somewhere. Mr. Geiser has a couple of charts he's requesting we show.

Dr. Delgado very briefly and Mr. Golenski very briefly.

Mr. GOLENSKI. Okay.

Ms. DELGADO. All right. I'm a clinical psychologist also in private practice licensed in the District. I work with an internist. My specialty is patients who have depression. And I can tell you that when people talk about therapeutic substitution there's a wide range. And that those decisions need to be made.

I don't make them. I work with someone who prescribes and sees patients and does that. And he works with the patient to do that. And I'm very concerned about creating a system where everyone says cheaper is better. Cheaper is not better. Cheaper may be better, but let that be based on the individual patient and their provider.

And as for cost, just like we like to have seat belts and that was an added cost for the consumer, it did save lives. I think we have to be very careful about just focusing on cost.

Mr. BILIRAKIS. If the provider were to prescribe a generic, that's the provider doing it, right?

Ms. DELGADO. But it didn't work. Then they should have the ability to give the patient something else. What happens is when Congress says this is how we're going to do and this is what we're going to pay, all those other drugs get taken off the list and you can't give them to patients. And I can tell you, I treat people with depression. Some of them do well with one, some with another and you have to change until you find the right medicine for the person.

And it's just inconceivable to me to put that decision away from the specific patient and provider. That's not the way—and formularies. I mean——

Mr. BILIRAKIS. So what you're saying is when we do the prescription drug for seniors among the Medicare Act, that we should take all that into consideration?

Ms. DELGADO. Especially since we know since it was only 2 years ago that FDA said companies had to start keeping records on people over 75 when they were doing their drug trials. Since most people—the fastest growing segment of the population is people over 80 we need to know.

Mr. BILIRAKIS. Isn't what you're saying and what Dr. Glover said also applicable to brand name drugs?

Ms. DELGADO. Sure.

Mr. BILIRAKIS. So it's not just generics, is it?

Ms. DELGADO. No, my thing is——

Mr. BILIRAKIS. It might react——

Ms. DELGADO. My thing is the decision is between the patient and provider based on effectiveness. If you'll notice in the language when we talked about generics is we want the outcome to the patient to be the same. Not that it's the same absorption rate, that's good. That's not enough. If it's absorbed the same, but the reaction to the patient is not the same, that's what I'm concerned about.

Mr. BILIRAKIS. Mr. Golenski, very briefly do you have anything you wanted to add?

Mr. GOLENSKI. Yes, quite specifically to that, Mr. Chairman. RxHealthValue strongly endorsed the Schumer-McCain and Brown-Emerson Bills. And the reason we did that is because we believe that cheaper is not better; cheaper is the same. And we realized that therapeutic and bio-equivalence is determined by the FDA. In addition to that, we have memberships representing 75 health plans in the United States. Some of them are nonprofit health plans. We have two large pharmacy benefit management organizations. And they all have generic substitution programs aggressively in place. We have no evidence of negative outcomes to the patients in generic substitution.

Mr. BURR. Mr. Chairman——

Mr. GOLENSKI. But the reason we endorsed those bills is because we believe cheaper isn't——

Mr. BILIRAKIS. But if there were evidence, you would like to know that a substitute would be available?

Mr. GOLENSKI. Well, we also aggressively support, of course, in all of these organizations that the physician and the patient are the people who make the determination of which medication the patient should be taking. But we'd like to have the generic available to the patient.

Mr. BILIRAKIS. Mr. Burr?

Mr. BURR. Mr. Chairman, I want to break the tie that you Mr. Brown had. Everybody here is right, but the reality is that we asked the FDA to be the gold standard for the approval process of pharmaceuticals, generics, medical devices in this country. And what we have done is we have created an atmosphere where it's tough for them to do their job because there's all sorts of legal attacks on different pieces. And it causes an agency like the FDA to sit back and look for an arbitrator or for the courts to make determinations. Unfortunately, the patient's the one that loses. Even though we're hearing different slices about where they can benefit and where they lose, and the reality is that if you want to maintain a gold standard—and I don't think that there's anybody here that's saying let's lower the bar. That's one of the reasons we can't harmonize our standards with the European Union. We can't do it around the world. Because we won't accept what they're willing to accept. We won't.

Mr. Golenski, we've been trying to do it for 6 years now. And the reality is that there's not too many people in America that want to adopt the standards that the Italians use, which is they use model because all members.

If we're going to maintain this gold standard, then the question is how do we make this system function? We were briefly on Waxman-Hatch Act. From a policy standpoint it is not perfect. It was not a policy document. It was political document. It's where different components of the industry gave in the waning hours up something, one got something, somebody gave up something, and it was their recommendation stay away from this.

It works pretty good right now. But when you look at it from a policy standpoint, it's certainly not perfect.

And I would only suggest to all of us that where we've got something to contribute that we think maintains the gold standard and presents a better option for patients across the country, present it. If it doesn't, then understand that we're not necessarily here to change the functions of the FDA. We had that opportunity in 1997. It was the FDA Modernization Act. We choose to maintain the standard, and I don't think there's willingness on the part of members to go back through and to change that standard.

I thank the chairman for the opportunity to editorialize. Let's see whether we can get a second set of questions.

Mr. BILIRAKIS. Mr. Geiser, I want to be fair. You can devote an all day hearing to each one of these subjects. We've crammed three in here. And we've got to try to limit, obviously, the gist of the issues. What we wanted to do in the case of the OTC was to try to determine whether in fact, as you heard, whether FDA has the authority and if they do have the authority, should they retain the authority to do it on a unilateral basis.

If you have charts toward that end, we would be glad to receive them. I would hope that it doesn't take much of an explanation. Are they so difficult to be able to understand that you'd have to explain them, because I don't want to delay this hearing much longer.

Mr. GEISER. I think it can be explained in very, very short order, Mr. Chairman.

Mr. BILIRAKIS. Short order means what?

Mr. GEISER. In 1 minute.

Mr. BILIRAKIS. One minute. And you would explain those?

Mr. GEISER. Yes, I will do that.

Mr. BILIRAKIS. If there's no objection, let's do that.

Mr. GEISER. The two charts speak to this question of access to care and to make it clear as the committee is considering this topic to inform the committee's consideration as to what we believe the outcome of the OTC switch would be.

This chart demonstrates, basically, the monthly cost of OTC products. Claritin OTC in the UK and Canada, and the current monthly cost on a prescription basis here in the United States.

The second chart demonstrates that we believe, and we cannot be certain of this, but if the OTC switch is granted and the drugs are marketed over-the-counter that these second-generation antihistamines will be offered at substantially monthly cost than is currently the case, that in fact that cost in addition to benefiting the uninsured and seniors or the people that are not covered, will in fact result in lower out-of-pocket cost for the insured.

We've shown here that our blended brand drug co-pay is about $17, this is just a blended average of our health plans everywhere. And for a physician office visit about $17 if you need a physician office visit to secure the prescription. So we're looking at even an insured member incurring substantially more out-of-pocket cost in comparison to what we anticipate a post-OTC switch price of these drugs will be.

Mr. BILIRAKIS. Do you have those charts in the form that we can put them into the record?

Mr. GEISER. They are attached to my statement.

Mr. BILIRAKIS. They are attached. Without objection, it will be made a part of the record Mr. Brown.

Mr. BROWN. Well, without prolonging the debate, I will speak even shorter than Mr. Geiser. And I just wanted to comment on something Dr. Delgado said. She over and over from her written testimony through several questions talked about quality and not worrying so much about price. And I agree with that. I think we all do. But, you know, this is a Congress unwilling to spend money on prescription benefit. It's a Congress unwilling to spend money on universal coverage. It may, I hope not, but be a Congress unwilling to spend money on the speeding up the approval process for ANDA. But a Congress that gives tax cuts to the richest people in the country——

Mr. BURR. I take back those nice things I said about your earlier.

Mr. BROWN. But, you know, the fact is that overshadows, that's an umbrella on everything we do here; on universal coverage, on prescription drug prices. on prescription drug coverage. And I would hope that you would use the National Alliance for Hispanic Health to push for that, because we can't have the quality of healthcare that you keep talking about if we're unwilling to pay for it.

Ms. DELGADO. I agree, but part of it is when you talk about costs you have to talk about the cost saving of keeping somebody out of the hospital.

Mr. BROWN. Of course you do.

Ms. DELGADO. That's also the other side of it.

Mr. BROWN. We don't think in those terms——

Ms. DELGADO. I'm with you. I'm here. Don't worry.

Mr. BILIRAKIS. Dr. Delgado, all legislation we have up here is costed by the Congressional Budget Office.

Ms. DELGADO. I understand.

Mr. BILIRAKIS. And you know what? They do not give us ever any credit for preventative healthcare or the keeping them out of the hospital unfortunately.

Ms. DELGADO. Right.

Mr. BILIRAKIS. And that makes our job so much more difficult.

Ms. DELGADO. But we're with you.

Mr. BROWN. Wrap it up, Mr. Chairman.

Mr. BILIRAKIS. Yes. We customarily ask if you would be receptive to, I haven't heard anybody ever say no. If you said no, I'm not sure what we could do about it. But we would like to furnish you with written questions and ask you for your written response within a matter of just a few days or so. We appreciate it.

Thanks so much for your patience. Thanks for sitting here through a couple of votes. You've been an awful lot of help.

[Whereupon, at 2:15 p.m. the hearing was adjourned.]

[Additional material submitted for the record follows:]

PREPARED STATEMENT OF ALLERGY & ASTHMA NETWORK MOTHERS OF ASTHMATICS

As a patient advocate and the founding president of Allergy & Asthma Network Mothers of Asthmatics (AANMA), I am writing to oppose OTC status of nonsedating antihistamines due to lack of tangible evidence that patients can use these medications safely without physician diagnosis or guidance. In the absence of such compelling data, the FDA should not grant OTC status for nonsedating antihistamines.

For the last four years and with support from more than 100 members of Congress, AANMA has conducted an annual Asthma Awareness Day on Capitol Hill. We've worked to make members of Congress aware of the issues that affect patient

lives and to promote patient access to improved medications, specialty care, school nurses, and medications while on school property.

Allergies and asthma are increasing at epidemic rates in our country and no one knows why. While NIH, EPA, HHS, CDC, AANMA, and others work tirelessly to reach underserved populations suffering with these conditions, health insurers (companies *we pay to insure our health*) lobby Congress and the FDA to transfer their financial burden for these medications to the backs of patients and families.

If health insurers want to save money, place patient outcomes first. Don't whittle away at our benefits. We want to be well at home, work, school, and play.

Take the case of the harried father at CVS whose tiny, glassy-eyed, frail daughter coughed relentlessly at his side while he struggled to read the packaging of a combination cough and antihistamine medication. He looked at me and said, "You are a mom. What do you give a little girl who can't stop coughing?" I said, "A trip to the doctor's office."

The father snapped back, "I'm not going to give one more dollar to those money-grubbing b----," then took four different cough preparations to the checkout counter.

Is this father safely using OTC medications? No. Will more choices lining the store shelves help? No.

If nonsedating antihistamines cannot be safely and strategically introduced in today's market so that all people can make informed purchases, then patients and parents of children with allergies and asthma are not ready for OTC nonsedating antihistamines.

OTC medications have their place on store shelves across America, but not without the evidence that patients can safely use them. Drug safety and patient use safety are one and the same on the OTC market.

PREPARED STATEMENT OF THE NATIONAL ASSOCIATION OF CHAIN DRUG STORES

The National Association of Chain Drug Stores (NACDS) appreciates the opportunity to submit a statement for the record on Federal and state policies affecting the availability of generic pharmaceuticals. NACDS membership consists of nearly 180 retail chain community pharmacy companies that operate over 33,000 retail community pharmacies with annual sales totaling over $400 billion. Chain operated community retail pharmacies fill over 60 percent of the 3 billion prescriptions dispensed annually in the United States.

GENERIC DRUGS SAVE PATIENTS MONEY

Generic pharmaceuticals are a cost-effective way of providing prescription drug therapy. Pharmacists in community-based practice settings work with patients and physicians to maximize the use of lower-cost generics when they are available on the market. The savings from using generics are unmistakable. If a generic substitute is not available, a pharmacist works with the physician to determine if the patient can take a generic version of another drug.

With billions of dollars in brand name drugs coming off patent over the next few years, we believe that it is critical that any new Medicare drug benefit have both patient and pharmacy incentives to encourage greater generic use. We are concerned, however, about some of the tactics being used by brand name companies that may delay the availability of many of these lower cost generics, and thus raise costs for all prescription drug users.

According to IMS Health, the average brand-name prescription drug price was about $65.29 in 2000, while the average generic prescription drug price was about $19.33, less than a third of the brand price.[1] Because the average cost of a brand name prescription has escalated so rapidly over the last 10 years, the gap between the average brand name and generic prescription price has significantly widened. In 1990, the average gap was about $16.87. In 2000, that gap had almost tripled, increasing to about $46.

Although more generic drugs are on the market today, the percent of all prescriptions being dispensed with low-cost generic drugs has remained relatively flat over the last few years, about 42 percent of all prescriptions. However, despite this relatively stable trend in the dispensing of generic drugs, the share of all generic prescription dollars as a percent of total prescription dollars has decreased significantly. For example, in 1995, generic drugs accounted for 12.2 percent of all prescription sales; today, they represent only 7.1 percent.

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[1] Data presentation given by IMS in April 2001.

GENERIC DRUGS ARE SAFE AND EFFECTIVE

In almost all states, a pharmacist can dispense a generic drug, unless the physician has specifically stated in his or her own handwriting that the brand name pharmaceutical is "medically necessary." We encourage and support laws that leave the substitution of generic drugs to the professional discretion of the pharmacist.

However, in some states, generic substitution is prohibited for certain drugs, unless the pharmacist expressly obtains the permission of the physician, regardless of what the prescription states. Some states have passed these laws in response to misrepresentations by brand name drug companies regarding the safety of generic versions of their drugs. These are so-called "narrow therapeutic index" drugs, such as Coumadin or Theophylline, where the brand name manufacturer argues that the potential for problems for the patient from switching from the brand to a generic are so great that only a physician should authorize the switch. This obviously reduces the generic substitution rate of the drug.

Policymakers should be aware, however, that the Food and Drug Administration (FDA) has compiled a list of every prescription drug produced by every manufacturer including all information about safety and effectiveness for patients. The FDA exhaustively compared all generics to all brands and developed a directory, commonly called the "Orange Book," available to every pharmacy that lists which drug products are truly equivalent. In fact, the FDA Commissioner has said, "*...be assured that if the FDA declares a generic drug to be therapeutically equivalent to an innovator drug, the two products will provide the same intended clinical effect*".

The importance of assuring maximum access to generic drugs is important for a very simple reason. Savings from generic substitution should significantly increase when several high-volume brand name drugs come off patent in the next twelve months. According to IMS America, brand-name drugs with $8 billion in sales are scheduled to come off patent next year, and drugs with about $25 billion in retail sales are scheduled to come off patent between the years 2002-2005. Importantly, some brand name drugs within the anti-depressant and cholesterol-lowering therapeutic classes come off patent in the next year.

The potential for savings from the use of generics in these categories is significant, since public and private payors spent billions of dollars on anti-depressants and on cholesterol-lowering drugs last year.

COMMUNITY PHARMACIES DISPENSE MORE GENERICS THAN PBMS, MAIL ORDER

The use of generic drugs varies significantly by the source of prescription coverage. For example, generic drugs are used in about 55 percent of all prescriptions provided by community pharmacies to cash-paying customers. However, the percentage of generic pharmaceuticals used in private third-party plans and PBM coverage programs is much lower. In fact, the generic substitution rate for all mail order prescriptions is only 32.5 percent, while it is only 44 percent for all prescriptions paid by PBM or third-party prescription coverage plans.[2] Both patients and providers should be given incentives to use and dispense generic drugs in any new senior Medicare pharmacy benefit. These would include lower generic copays, as well as reimbursement incentives to the pharmacy to dispense generic drugs.

There are many factors that affect the ability of pharmacists to dispense generic drugs. These include state pharmacy practice laws; incentives used by third party plans to encourage generic use, such as lower copays and pharmacy generic dispensing fees; and the rebates paid by brand name manufacturers to third party payors, including mail order, to dispense brand name drugs rather than lower-cost generics.

Unfortunately, brand name manufacturer rebates have created perverse incentives for third party payors to switch from one expensive brand name drug, for which the plan does not receive a rebate, to a brand name drug for which they receive a rebate. The plan should be switching to a lower-cost generic. However, because generic manufacturers do not pay rebates and these payors make much of their money from these rebates, there is significant over-utilization of brand name drugs and under-utilization of generic drugs.

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[2] NACDS Analysis of 1996, 1997 MEDS data and NAMCS data. In addition, according to Brenda Motheral, Senior Director of Research for Express Scripts, generic fill rates are noticeably higher for retail than mail, as reported in "Pharmacy Benefit Design: What We Have Learned," April 6, 2000.

BRAND NAME MANUFACTURERS' TACTICS LIMIT GENERIC DRUG AVAILABILITY

Ultimately, a generic cannot be used unless it is available on the market. We are very concerned that some brand name manufacturers are employing multiple schemes to delay the availability of generic versions of their drugs, contributing unnecessarily to health care costs, increased spending for Medicaid, private prescription drug programs, and millions of seniors and uninsured individuals.

NACDS believes that brand name manufacturers should have appropriate incentives to research and develop new pharmaceuticals, and have sufficient marketing exclusivity time to allow them to recoup their investment with an appropriate profit. We do not believe, however, that many of these schemes are defensible, and we believe appropriate action should be taken by policymakers to correct these abuses.

For example, we are concerned with the abuses that have developed surrounding the awarding of the 180-day exclusivity provision for the generic company that successfully challenges a brand name patent; the practice of some brand name companies to "late list" patents in the Orange Book, resulting in a 30-month stay of the generic drug approval; and the filing of frivolous "citizens petitions" with the FDA, which slows down generic drug approval. These citizen petitions can delay generic availability for six to eight months, and the overwhelming majority of them are rejected by the FDA.[3]

For these reasons, *we support* H.R. 1862, and its companion bill S.812, the "*Greater Access to Affordable Pharmaceuticals Act*," also known as the Emerson/Brown and McCain/Schumer bills. We look forward to working toward its enactment.

We also support the FTC's investigation into the extent to which brand manufacturers have paid generic manufacturers not to market competing generic drug products. The FTC also plans to investigate brand manufacturers' abusive patent listings and patent litigation, which stall generic competition, whether or not the listed patents are valid.

After the FTC completes its study, we recommend implementation of a four-stage strategy with the goal of preventing such anticompetitive practices in the future.

- First, the FTC should immediately halt all anticompetitive practices it discovers.
- Second, the FTC should issue new rules or guidances preventing such anticompetitive arrangements in the future.
- Third, the FTC should work closely with the Food and Drug Administration to revise the FDA's policies regarding citizens' petitions, the 180-day exclusivity rule and the 30-month stay rule.
- Fourth, the FTC should recommend revisions to the relevant provisions of the Hatch-Waxman Act to permanently eliminate the ability of brand and generic drug manufacturers to conspire to restrain competition.

We are also concerned with certain brand-name manufacturer "evergreening" strategies, which, when combined with the explosion in direct-to-consumer (DTC) advertising, are further minimizing the cost savings impact of generics, even if they are successful at reaching the marketplace.

For example, before a patent expires on a brand name drug, a manufacturer will seek to switch the patient to a slightly-different "next generation" of the brand name drug, or seek to move the patient over to a long-acting or single-day dosage of the drug, making it difficult for the generic to penetrate the market. This process has been made easier by DTC advertising, which encourages patients to ask their physicians about new drug therapies. While we believe that some patients would logically benefit from the new generation drug, or the new daily dosage form, it is highly likely that the patient could use the generic version of the brand name drug and experience the same medical results at a much lower cost.

We are also concerned about a new "evergreening" tactic in which a brand name company seeks a different "use patent" for a drug whose original patent is about to expire, and sells the drug under a different name and for a different indication. Even though the original product may be off patent, the pharmacist cannot substitute the generic version of the off patent brand for the identical new patented drug because of the new use patent that the manufacturer was successful in obtaining. Take, for example, Sarafem, which contains the same active ingredient as the popular anti-depressant Prozac, but which was approved for the new use indication of premenstrual dysphoric disorder (PMDD).

Finally, we understand that the Congress will be reauthorizing the pediatric exclusivity provisions of the FDAMA this year. NACDS fully supports the testing of drugs in children, and believes that it is important that many older, off patent drugs, which are commonly used in children today, should be among those tested.

[3] Wall Street Journal, November 1998.

However, we question whether the six-month additional exclusivity afforded to some block buster drugs is an appropriate public policy incentive to encourage brand name companies to do these studies. Pharmaceutical companies should be rewarded for doing these studies, but it may be the case that the hundreds of millions of dollars in additional revenue generated for these manufacturers in brand name drug sales are skewed in favor of drug manufacturers rather than consumers. The value of this exclusivity should be directly tied to the value and usefulness of the pediatric studies. Moreover, this additional six months gives manufacturers additional time to execute their various "evergreening" strategies, which further delays generic entry and erodes generic penetration.

CONCLUSION

NACDS strongly urges Congress to examine current laws and regulations that determine the market availability of generic pharmaceuticals. It is critical for life and health that brand name manufacturers are given appropriate incentives to research and develop new drugs and to study the effects of drugs in children. On the other hand, it is also necessary to assure that generic pharmaceuticals know the "rules of the road" without being hit with every detour and delay that a brand name manufacturer can use to limit the availability of generic drugs. We think that the current market is out of balance, and generic availability and the savings to consumers is the primary casualty of this brand name drug bias.

We believe that Congress should act soon to rectify this situation. Undoubtedly, increasing the availability of generic drugs will help make a new Medicare senior pharmacy benefit more affordable, as well as help struggling state Medicaid programs control their drug spending. We also believe that this will help uninsured Americans better obtain their medications and slow the rate of growth in private sector drug programs, which have also been experiencing double-digit rates of growth in their pharmaceutical budgets. We appreciate the opportunity to submit this statement for the record. Thank you.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

July 11, 2001

VIA MESSENGER

The Honorable John D. Dingell
U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

Dear Representative Dingell:

Thank you for the opportunity to testify before the Subcommittee on Health on June 13, 2001. As you requested, enclosed are supplemental responses to the questions presented by your office, dated June 26, 2001.

I would be pleased to answer any additional questions you may have, or to work with this Subcommittee, the Congress, and the Administration to see that the original balance struck by the Waxman-Hatch Amendments is restored.

Sincerely,

Bruce L. Downey

Bruce L. Downey
Chairman & CEO
Barr Laboratories, Inc.

Enclosure

cc: Kristi Gillis
Clerk of the Committee on
Energy & Commerce

DC-455687 v1 0306556-0100

Barr Laboratories, Inc.

Question 1: On the topic of bioequivalence, you agreed with the agency's position and, thus, took issue with PhRMA's testimony. Please explain your concerns with respect to PhRMA's testimony on this issue. Also, please address the issue of metabolic differences in ethnic groups and how these do or do not effect substitutability

On behalf of GPhA, I oppose PhRMA's testimony on bioequivalence. Through its testimony, PhRMA seeks to undermine the public's confidence in the therapeutic equivalence of generic drugs by casting doubt on FDA's bioequivalence standard. PhRMA referred to FDA's statistical criteria in its testimony as if it were arbitrary and overly broad. In fact, nothing could be further from the truth. FDA's bioequivalence standard is the result of more than 30 years of intensive scientific studies by hundreds of pharmaceutical scientists, research physicians, biostatisticians, and other scientific experts.

In statistical terms, FDA's bioequivalence standard can be stated as a requirement that the 90% confidence intervals for the geometric mean test/reference ratios of the area under the plasma concentration versus time curve (AUC) and the maximum plasma concentration (C_{max}) fall within the range of 80% to 125%. PhRMA has seized upon this complex statistical language to allege that FDA is misinforming the public about the equivalence of generic drugs. The facts, however, reveal that it is PhRMA, not FDA, who is misleading the public on this issue. FDA has undertaken to determine the actual differences between the generic and brand drugs that FDA has approved as equivalent since 1984. Those studies have shown that the actual variation between the bioavailability of the generic and corresponding brand drugs is approximately 3.5%. See Jane Henney, M.D., Review of Generic Bioequivalence Studies, J. Am. Med. Assoc. Vol. 282, No. 21, at 1995 (1999). In fact, the difference between an "A" rated generic drug and the corresponding brand product is similar to the difference between two manufacturing lots of the brand product (i.e., the same difference as between prescription refills of the brand product).

It is somewhat ironic that PhRMA has attacked the credibility of FDA's bioequivalence standard, in light of the fact that brand companies frequently use the standard to obtain approval of new formulations, other application changes, or even their own generic products. In fact, it has been suggested that if FDA tightened its standards as PhRMA suggests, some of the product reformulations sought by brand companies could not be approved without efficacy studies. Similarly, it is important to note that a high percentage of the generic drugs marketed in the U.S. are manufactured by brand companies or their subsidiaries. It is, therefore, hard to reconcile PhRMA's position on this issue. On the one hand, they accept FDA's standard as sound science when it results in faster approval of their new formulations and generic products; yet, on the other hand, they denounce it when it results in competition from affordable pharmaceuticals.

Lastly, with respect to metabolic differences in ethnic groups, it is important to note that this is not a "generic" issue, but is one that is important to both brand and generic manufacturers. In most cases, any metabolic differences will similarly affect both the generic and brand products. Once it is established that the active moiety in the generic and brand drugs are available at the site of action in equivalent concentrations, the two drugs will normally be similarly metabolized in the various ethic populations. While there are certainly exceptions to this general rule, they are rare and FDA deals with exceptions on a case-by-case basis.

Barr Laboratories, Inc.

Question 2: Do you agree with the agency's position that the Food and Drug Administration lacks a regulatory pathway for biologics approved under the Public Health Service Act.

Both the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHSA") provide clear authority to the Food and Drug Administration ("FDA") to approve generic versions of biologic products, and to make therapeutic equivalence determinations for such products. While that authority has always existed, Congress clarified its intentions in sections 123(f) and 123(g) of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"). Section 123(f) instructs FDA to minimize the differences in the review and approval of drugs under the FDCA and biologics under the PHSA. Section 123(g) states that "biologics" licensed under the PHSA are also "drugs" under the FDCA, and that an approved FDCA application is no longer required for products that are licensed under the PHSA. See 42 U.S.C. § 262(j). When these two provisions are considered in tandem, and interpreted in light of the deference granted to agencies under the *Chevron* doctrine, a very strong case for FDA's authority to approve generic biopharmaceuticals under the FDCA emerges from the statutory text.

Although it may be possible for FDA to approve abbreviated new drug applications ("ANDAs") for generic biopharmaceuticals, the provision of the FDCA most amenable to the approval of these products is section 505(b)(2). This provision gives FDA the authority to approve new drug applications ("NDAs") for drug products based on published literature and/or information contained in approved applications. As clearly noted in Section 123(g) of FDAMA, biologics are "drugs" which can be the subject of an NDA. The current statutory language, therefore, provides ample authority for FDA to approve a 505(b)(2) NDA for a generic biologic (i.e., "drug") product based on a determination that it is comparable to an approved or licensed product.[1]

The 505(b)(2) process appears to be particularly well suited from drug products that are similar to "well characterized" biopharmaceuticals. Moreover, for other complex agents, FDA could determine the appropriateness of the 505(b)(2) process for a given product on a case-by-case basis. Where the science and technology is such that comparability can be scientifically established, FDA could make a therapeutic equivalence determination for a "generic" biopharmaceutical approved under the FDCA and the "brand" biologic licensed under the PHSA. Lastly, FDA has historically made therapeutic equivalence determinations as a "service" to the medical community and the States. There is, therefore, no reason why FDA could not provide its opinion on whether the application supports the interchangeability of the generic biopharmaceutical.

[1] We note, however, that doing so would require FDA to revoke an antiquated regulation that prohibits the filing of NDAs for products that are subject to licensure under the PHSA. See 21 C.F.R. § 314.101(e)(1).

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Response to Questions from Representative Dingell
for the record of the hearing on
"Recent Developments Which May Impact Consumer Access To,
And Demand For, Pharmaceuticals"
Wednesday, June 13, 2001
Subcommittee on Health
Subcommittee on Energy and Commerce
U.S. House of Representatives, Washington, D.C.

Responses to Questions for Dr. Glover
presented as an attachment to a letter
from Representative Dingell, dated June 26, 2001

On behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA), I appeared before the Subcommittee on Health on June 13, 2001. My written and oral testimony focused on the operation of the Hatch-Waxman Act.[1] In particular, my testimony emphasized that the Hatch-Waxman Act has created a pharmaceutical market in the United States that benefits consumers and patients, as Congress intended when it passed the Act in 1984. Accordingly, the major changes to the Act that are being advocated by generic manufacturers are not necessary and would jeopardize future innovation.

The Questions from Representative Dingell for the record of the hearing (Follow-Up-Questions) address three areas: (1) pioneer/generic bioequivalence; (2) the proportion of

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[1] The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to by the names of its principal sponsors in the Senate (Orrin Hatch) and the House of Representatives (Henry Waxman).

generic applications that have raised patent infringement issues; and (3) research and development expenditures by the innovator pharmaceutical industry.[2]

I. Pioneer/Generic Bioequivalence

The first Follow-Up Question concerns the variation in bioavailability between generics and their pioneer counterparts. I testified that the Food and Drug Administration (FDA) permits as much as a plus or minus 20 percent difference in the bioavailability of a generic in comparison to a pioneer, thereby allowing for a possible 40 percent differentiation between one generic and another.

Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research (CDER), had stated earlier that "the data shows an average brand to generic variation of less than three percent, no different from an innovator drug tested against itself day-to-day or lot-to-lot." In addition, Mr. Bruce L. Downey, testifying on behalf of the Generic Pharmaceutical Association, stated that "the FDA bioequivalence standards are the same that innovator firms use to determine bioequivalence when they scale up or otherwise change production methods." Understanding the real and perceived differences in these statements requires a careful analysis focusing on observed averages, confidence intervals for the difference of the averages (percent deviations around the observed averages within which a true average resides), and permitted variations between observed averages.

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[2] The complete text of the Follow-Up Questions is included as Attachment A.

A. Pioneer/Generic Variations

Since the measured plasma drug level for a drug will vary from measurement to measurement, the plasma drug level for a drug will be described in terms of the average plasma drug levels and an interval which will have a 90% chance to include the true average difference in plasma drug levels (90% confidence interval). That is, if multiple comparison studies were conducted, approximately 90% of observed average differences will reside in this interval. Accordingly, there will be an upper bound to the 90% confidence interval and a lower bound to this confidence interval.

FDA's guidance permits the 90% confidence interval (*i.e.* the range from the lower to the upper bound of the confidence interval) for the plasma drug concentration for the generic drug to fall anywhere between -20% and +25% of the average plasma drug concentration of the pioneer product.[3] This means that FDA would permit the plasma drug concentrations of any given lot of the generic drug within the 90% confidence interval to be up to 20% less than the pioneer or up to 25% more than the pioneer.[4] According to this FDA guidance, any generic products with a 90% confidence interval that falls within this -20/+25% range would be considered bioequivalent to the pioneer drug.

This substantial deviation around the average plasma concentrations of the pioneer product means that a particular lot of Generic 1 (G1) at the low end of the range could result in blood levels 20% less than the pioneer and more than 35% less than a lot of Generic 2 (G2) when G2 is 125% of the pioneer product and G1 is compared to G2. In the alternative, a lot

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[3] See FDA Guidance entitled, Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design, Center for Drug Evaluation and Research (July 1992).

[4] Moreover, these limits apply only to the 90% confidence interval. Ten percent of the individual plasma drug concentration measurements might be outside this range.

of G2 could result in a plasma drug concentration 25% greater than the pioneer and more than 55% greater than a lot of G1 when G2 is compared to G1.[5]

B. Bioequivalence Standards for Innovator Companies

As Mr. Downey indicated, innovator companies use a standard for bioequivalence for scale up of manufacturing or changes in production. This bioequivalence standard also requires the 90% confidence interval around the average plasma drug concentration of the product produced after the manufacturing change to fall completely within -20/+25% range of the average of the plasma drug concentration of the original product.

The principal difference between this pioneer-pioneer bioequivalence and generic-generic bioequivalence is as follows. In pioneer-pioneer bioequivalence, the maximum theoretical difference in the boundaries of the 90% confidence interval for plasma drug concentration of the pioneer produced after the manufacturing change will be ***either*** 20% less than the pioneer ***or*** 25% more than the pioneer. In contrast, the maximum theoretical difference in the boundaries of the 90% confidence interval for plasma drug concentrations between different generics for the same pioneer – one which can be 20% less than the pioneer and the other which can be 25% more than the pioneer – can be more than 50%, a markedly broader potential difference. In pioneer-pioneer bioequivalence, the theoretical difference varies only between the average and one boundary of the bioequivalence range (*i.e.*, from 0 to –20% less than the pioneer or from 0 to +25% more than the pioneer) whereas with generic-generic bioequivalence, the theoretical difference varies across the entire range of the two extremes (*i.e.*, from –20% less than the pioneer to +25% more than the pioneer).

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[5] The numerical differences in percentages results from using the low end of the permissible range as the starting point in one case and using the high end of the range as the starting point in the other case.

C. Generic Bioequivalence Studies

FDA has conducted two meta analyses[6] to pool information from many studies. Both studies show that the average difference in plasma drug concentration between pioneer and generic drugs is approximately 3.5%.[7] These studies reviewed 127 *in vivo* bioequivalence studies in 273 generic drug applications approved in 1997 and 224 *in vivo* studies in applications for generic drugs that were approved from 1984 through 1986. Although the observed average difference from this meta analysis is 3.5%, if one considers the variation about this difference, this number may be higher.

Moreover, even if it were appropriate to extrapolate the results of fewer than 400 studies to the thousands of *in vivo* bioequivalence studies that have been submitted to FDA in generic drug applications, the industry remains concerned about the very large range over which FDA would permit a finding of bioequivalence between a generic and a pioneer drug. The small average difference in plasma drug concentrations does not diminish the research-based industry's concerns that FDA's bioequivalence standards continue to permit these wide variations from the average plasma concentration levels of the pioneer product.

Moreover, the FDA studies do not address the existence of large variations in plasma drug concentrations for multiple generic products that correspond to the same pioneer products. Indeed, the FDA study on applications approved from 1984 through 1986 confirms that some generic products are approved when the average plasma drug concentration is near one

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[6] It should be noted that statisticians have raised a number of concerns about the validity of this type of analysis.

[7] Nightingale SL, Morrison JC. Generic Drugs and the Prescribing Physician. JAMA 1987; Vol 258: No 9 (Attachment B); Henney JE. Review of Generic Bioequivalence Studies. JAMA 1999; Vol 282 No 21 (Attachment C).

of the extremes of the –20%/+20% range[8] with respect to the average plasma drug concentration of the pioneer. Thus, if two generics for the same drug were deemed to be bioequivalent based on plasma drug concentrations at the extremes of the –20%/+25% range when comparing the generic product to the pioneer reference product, the consumer would face the wide variation in generic-generic bioavailability that concerns the pioneer industry. This could lead to significant clinical risks for patients switched from one generic product to another. Accordingly, it is not clear why FDA continues to permit the large range of acceptable variations in plasma drug concentrations that would permit a determination of pioneer-generic bioequivalence.

II. Patent Issues in Generic Product Applications

The second Follow-Up Question concerned the number of patent issues that have been raised in the generic drug applications that have been approved in 1984. I testified that "of more than 8,000 generic applications that have been filed since 1984, fewer than 500 have raised any patent issues." Information regarding the number of generic applications that have raised patent issues was derived from a speech by Cecelia M. Parise, R. Ph., Special Assistant for Regulatory Policy in CDER's Office of Generic Drugs at FDA.[9]

FDA's reported information indicates that since 1984, 8,259 generic applications were filed with FDA. Of those applications, 7,781 – 94 percent – raised no patent issues. These

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[8] At the time of the first FDA study, the permissible variation from the average plasma drug concentration of the pioneer was –20%/+20% rather than the current –20%/+25%. Nightingale and Morrison, JAMA 1987; Vol. 258: No. 9 (Chart at 1202) (Attachment B).

[9] Cecelia M. Parise, R.Ph., Special Assistant for Regulatory Policy, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Update: 180-Day Generic Drug Exclusivity for ANDAs and Patent Listing, presented at the March 20, 2001, NAPM meeting, at Slide 10. Slides from that presentation are available at http://www.fda.gov/cder/ord/Exclusivity/.

applications certified either that: (1) no patent information had been filed by the innovator; (2) the patents listed had expired; or (3) the patents listed would expire prior to marketing the generic product.

Accordingly, only 478 generic drug applications – 5.8 percent – asserted that a listed patent was invalid or would not be infringed by the marketing of the generic product. FDA's published information does not include statistics on the number of chemical entities, dosage forms, characterizations of patents (as either primary or otherwise), or sales of products. Similarly, PhRMA does not have this information.

III. Research and Development Expenditures

The third Follow-Up Question concerns the amount of research and development expenditures compared to marketing expenditures and Direct-to-Consumer Advertising. I testified that the research-based pharmaceutical industry will expend more than $30 billion this year in research and development. The third Follow-Up Question requested information that would permit a comparison between the research-based industry's expenditures on research and development and the industry's expenditure for total product marketing and for Direct-to-Consumer Advertising.

I have attached charts that illustrate research and development spending in comparison to marketing spending for the last five years (Attachments D, E, and F). These charts are based on information from IMS Health, Inc. and PhRMA. The data demonstrate that research and development expenditures exceed marketing expenditures by 40 percent. Moreover, from 1996 through 2000, the average expenditure for total marketing was $12.5 billion. Approximately 52% of that total marketing expenditure was spent on free samples to physicians and patients, thereby leaving about 35% for professional marketing expenditures and

12% for Direct-to-Consumer marketing expenditures. Accordingly, Direct-to-Consumer marketing expenditures are only 7% of the expenditures for research and development.

Finally, it is worth noting that some advocacy groups have misstated the comparison between research and development spending and marketing expenditures by basing the latter figures on annual report data, which typically includes a combined figure for marketing ***and administrative*** expenses.

* * *

I would be pleased to answer any questions or to supply any additional materials requested by Members or Committee staff on these or any other issues.

Sincerely,

Gregory J. Glover

Dated: July 11, 2001

Attachments

Attachment A

06-27-01 10:23am From-COMMERCE CMTE DEMOCRATIC STAFF + T-425 P.01/03 F-670

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TOM DAVIS, VIRGINIA
ED BRYANT, TENNESSEE
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JOHN D. DINGELL, MICHIGAN
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DAVID V. MARVENTANO, STAFF DIRECTOR

One Hundred Seventh Congress

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

W.J. "BILLY" TAUZIN, LOUISIANA,
CHAIRMAN

June 26, 2001

Gregory Glover, M.D.
Partner
Ropes & Gray
1301 K Street, N.W., Suite 800
Washington, D.C. 20005

Dear Dr. Glover:

I appreciate your testimony before the Subcommittee on Health on June 13, 2001. I have additional questions for which I request a response for the hearing record. Please respond to the attached questions by Wednesday, July 11, 2001.

Thank you for cooperation in this matter. If there are any questions please contact John Ford or David Nelson with the Committee on Energy and Commerce Democratic staff at (202) 226-3400.

Sincerely,

JOHN D. DINGELL
RANKING MEMBER

Attachment

cc: The Honorable W. J. "Billy" Tauzin, Chairman
Committee on Energy and Commerce

The Honorable Michael Bilirakis, Chairman
Subcommittee on Health

The Honorable Sherrod Brown, Ranking Member
Subcommittee on Health

Questions from Representative Dingell
for the record of the hearing on
"Recent Developments Which May Impact Consumer Access To,
And Demand For, Pharmaceuticals"
Wednesday, June 13, 2001
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives, Washington, D.C.

Questions for Dr. Glover

1) You testified that the Food and Drug Administration (FDA) permits a wide variation, as much as plus or minus 20 percent of the bioavailability, between generics and their brand counterparts and that this standard allows for a possible 40 percent differentiation between one generic and another.

a) May we assume this is not only your personal position but also that of the Pharmaceutical Research and Manufacturers of America (PhRMA) on whose behalf you testified?

b) Are you saying that generics could be 20-40 percent less effective than their brand counterparts?

c) Please provide a detailed discussion of FDA's bioequivalence criteria and your concerns with them.

d) Dr. Woodcock testified that generics can be freely substituted for the innovator or brand product. She went on to say that the data shows an average brand to generic variation of less than three percent, no different from an innovator drug tested against itself day-to-day or lot-to-lot. How do you reconcile your position and/or that of PhRMA with her testimony?

e) Why should the American public have faith in the FDA's assessment that innovator drugs are safe and effective when used as labeled, but no faith in the FDA's ability to make the same definitive judgment regarding the generic drug with the same active ingredient?

f) Do you believe that FDA cannot be relied upon to assure the same safety and efficacy profile for the "A" rated generic drugs as for the branded product?

g) Mr. Downey testified that the FDA bioequivalence standards are the same that innovator firms use to determine bioquivalence when they scale up or otherwise change production methods. Please explain the distinctions, if any, between the bioequivalence testing methods used by innovator and generic firms. If the methodologies are the same, why would one provide adequate assurance of bioequivalence among batches using differing production methods but not when comparing batches between two different manufacturers?

h) Please supply the Subcommittee with the scientific references that support your positions on each of questions (a) through (f) listed above.

2) You testified that "of more than 8,000 generic applications that have been filed since 1984, fewer than 500 have raised any patent issues." Of the 8,000 generic applications filed since the enactment of Waxman-Hatch:

a) How many separate chemical entities were involved (separate drugs regardless of dosage forms)?

b) How many involved tablets or capsules (as opposed to liquids or topical drugs)?

c) How many involved drugs whose primary patent expired after 1984?

d) Of the separate chemical entities that were in either tablet or capsule dosage form and whose patent expired after 1984, how many had sales exceeding $10 million last year or the last year before generic competition, whichever is applicable?

e) Of the drugs identified in (d) above, how many were subject to patent challenges?

f) Are there any of the 100 largest selling brand name drugs (by total revenue) still on patent? If so, how many have multiple patents with differing expiration dates?

g) Do you believe that any of the these 100 best selling drugs will incur generic competition upon expiration of the earliest patent without a patent challenge? If so, please identify the drugs and explain why you believe that the innovator will permit an uncontested generic entrant upon expiration of the earliest patent.

3) You have testified that R&D expenditures by the innovator industry reached or will reach $30 billion this year. Please inform this Subcommittee how much money the brand industry spent or will spend on product marketing this year. Further, please identify the amount of the industry marketing budgets spent on Direct-to-Consumer Advertising. It would be helpful if you could provide each of these figures in chart form for the past five years (Research, Marketing, and DTC advertising).

Attachment B

Special Communication

Generic Drugs and the Prescribing Physician

Stuart L. Nightingale, MD, James C. Morrison

While generic substitution is not a new phenomenon, a number of factors have combined to markedly increase generic drug use. The most important factor is a 1984 law, the Drug Price Competition and Patent Term Restoration Act, which facilitates the entry into the marketplace of generic versions of brand name drugs. This law and Food and Drug Administration (FDA) policies are designed to approve for marketing generic drug products that are therapeutically equivalent to their brand name counterparts. With increased availability of generic drugs, physicians have expressed the need for more information about the FDA process for determining that generic versions of brand name drug products are both safe and effective and that generic drug products will produce the same therapeutic results as those achieved by the brand name products. This article describes FDA procedures for approving generic drug products and examines issues important to the prescribing physician, in particular, therapeutic equivalence. The article also describes the role of the states in generic substitution and the availability of information from the FDA on the therapeutic equivalence of drug products.

(JAMA 1987;258:1200-1204)

A LIMITED number of generic drug products have been available for many years. A 1984 law, the Drug Price Competition and Patent Term Restoration Act[1] (referred to hereafter as the 1984 law), permits the Food and Drug Administration (FDA), through an expedited process called an Abbreviated New Drug Application (ANDA), to approve generic versions of "pioneer" or "brand name" drug products already found to be safe and effective by the FDA. The marked increase in the number of drug products now available as generics is most directly tied to this new law.

See also p 1216.

A major goal of the 1984 law was to facilitate the entry into the marketplace of generic versions of pioneer drugs whose patents had expired. By the end of 1986, generic versions were available for most of the ten top-selling prescription drugs on the market, as well as therapeutically equivalent generic versions of a host of other drugs. Two years after enactment of the law, some 1000 generic drug products had received FDA approval under the provisions of this new law. In addition to the 1984 law, several other developments in recent years have contributed to this increase in generic prescribing: the repeal of state antisubstitution laws; cost-containment initiatives by third-party payers; and finally, increased consumer awareness of generic drugs and responsiveness to the generic drug promotional efforts of large drugstore chains.[2,3] Although trends in generic drug prescribing are difficult to assess, according to one source, generic prescribing in 1985 increased by some 15% over the previous year.[4]

As there are more generic drugs on the market, and as prescribers and patients increasingly make use of generic drugs, physicians have expressed the need for more information about the review and approval of generic drug products. In particular, physicians have asked how the FDA determines that a generic version of a previously approved, brand name drug product is safe and effective and can, therefore, be approved for marketing. Physicians rightly demand assurances that the drug products they select for use in patients under their care have been thoroughly evaluated and that, if the drug products are available in generic versions, these generic products will produce the same therapeutic results as those achieved by the brand name product.

In this article, we describe in some detail the requirements and procedures employed by the FDA in the review and approval of marketing applications for generic drug products and, in that context, explore the various issues of concern to physicians considering the prescribing of generic drug products—most importantly, therapeutic equivalence.

FDA APPROVAL OF GENERIC DRUG PRODUCTS

Several key points regarding the review, approval, manufacture, and clini-

From the Office of Health Affairs (Dr Nightingale) and the Office of Drug Standards, Center for Drugs and Biologics (Mr Morrison), Food and Drug Administration, Rockville, Md.

Reprint requests to Office of Health Affairs, FDA, Parklawn Bldg, 5600 Fishers Lane, Rockville, MD 20857 (Dr Nightingale).

cal performance of generic drug products are important to keep in mind. First, differences between FDA criteria for determining the safety and effectiveness—and hence the approvability—of brand name and generic drugs are based on scientific considerations as well as the mandate to avoid unnecessary, duplicative studies. A second key point to be emphasized is that all approved drugs, both pioneer and generic products, must meet the same FDA standards for manufacture to ensure uniform quality. Third, generic versions of pioneer drug products must be bioequivalent to a degree, calculated statistically, so that products evaluated as therapeutically equivalent can be expected to have equivalent therapeutic effects and no greater potential for adverse effects. These are important considerations for physicians prescribing generic drug products.

The 1984 law and the FDA's generic drug policies are designed to approve for marketing only generic drug products that are therapeutically equivalent and of comparable quality to their brand name counterparts. Dispensing of a generic drug product that is therapeutically equivalent to the brand name product is known as generic substitution. All drug products that have the same active ingredient(s), dosage form, strength, and route of administration as the drug product originally introduced by the pioneer marketer are considered generic drug products. However, all generic drug products may not be therapeutically equivalent to their pioneer counterparts or to each other. Moreover, even therapeutically equivalent generic drug products may differ in characteristics such as color, flavor, shape, packaging, inactive ingredients, expiration time, and, within certain limits, labeling. The FDA evaluates as therapeutically equivalent those drug products that satisfy the approval criteria within the following three general categories: (1) product characteristics and labeling; (2) manufacturing and quality controls; and (3) bioequivalence. Information on how to identify those drugs rated by the FDA as therapeutically equivalent is given in the section below entitled "Therapeutic Equivalence List." The FDA recommends substitution *only* among products that are evaluated as therapeutically equivalent.

Product Characteristics and Labeling

An applicant for market approval of a generic drug product must show that both the proposed generic and the brand name drug product contain the same active ingredient(s) and are identical in strength, dosage form, and route of administration (eg, chlordiazepoxide hydrochloride, 5-mg oral capsules). Additionally, the labeling must be the same for both the brand name drug and the proposed generic drug product. One exception under the 1984 law is that the labeling for the generic product may omit a specific indication on which the pioneer manufacturer either holds a patent or has a three-year period of "exclusivity"—given under the 1984 law to reward the developer of a new use.

Manufacturing and Quality Controls

Large pioneer drug firms themselves account for an estimated 70% of the generic drug market.[4] Thus, large, research-oriented drug firms manufacture many generic products in addition to the drugs that they pioneered. Furthermore, a number of pioneer drug firms have purchased generic drug firms or distribute brand name drug products made for them by smaller generic firms.

Both brand name and generic drug products must meet the same FDA standards for chemistry, manufacture, and control. Detailed FDA regulations and guidelines specify the kinds of safeguards that must be used when manufacturing drug products so that acceptable quality can be assured. Inspectors from the FDA visit the manufacturing plant to determine whether the manufacturer has the capability and systems necessary to produce the drug product properly. Samples of drug products are randomly collected and tested in an FDA laboratory. All drug firms, brand name and generic, are subject to periodic inspection, and all must follow FDA Good Manufacturing Practice regulations, which touch on every aspect of making drugs from building maintenance to quality control. These requirements are intended to ensure that all drug products meet the same standards for purity, strength, and quality. That these safeguards work is evidenced by the fact that the rate of defects found by the FDA in both brand name and generic products is extremely low.[4] It should be noted, moreover, that brand name and generic firms are all under the same obligations to report adverse drug reactions as well as product defects to the FDA.

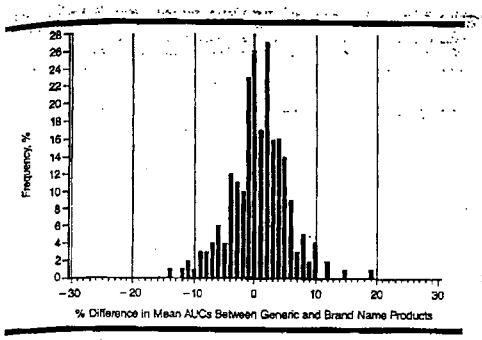
Bioequivalence

The applicant for marketing approval must show that the drug product for which the applicant is seeking approval is bioequivalent to the brand name drug (ie, that the proposed generic and pioneer drug products can be expected to have the same therapeutic effect when administered to patients under the conditions specified in the labeling). Usually the bioequivalence of drug products is established through studies in humans (in vivo tests) that measure the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product.

In certain situations, in vivo testing is not required to establish the bioequivalence of two products. For some older drugs that have appropriate physicochemical properties, that do not present a known or potential bioequivalence problem, and for which there is sufficient clinical experience, bioequivalence may be demonstrated by meeting an appropriate in vitro test (ie, dissolution). In still other cases, the bioequivalence of drug products may be inferred from the nature of the product, such as a drug product that is a solution (but not a suspension) for oral or intravenous administration.

In Vivo Testing and Criteria for Approval.—For systemically absorbed drugs, in vivo bioequivalence tests compare the ability of the proposed generic products to achieve comparable plasma levels of the active ingredient and, in some cases, their metabolites with those achieved by their brand name counterparts, when administered to the same individuals under as nearly identical conditions as possible. Because plasma levels commonly vary among different people receiving the same drug product and even among separate administrations of the same product to the same individual, both the generic and the brand name products are tested in the same individuals in a crossover study. The FDA makes a determination that two products are bioequivalent only when appropriate statistical criteria are met.

For FDA approval of a generic drug product based on in vivo bioequivalence test data, an applicant must show that its product does not deliver its active ingredient(s) to a significantly different extent or at a significantly different rate than does the brand name product. The experimental parameters measured in a bioequivalence study include the area under the drug concentration-time curve (AUC), which is indicative of the extent of absorption, and the maximum concentration (C_{max}) and the time of maximum concentration (T_{max}), which are both indicative of the rate of absorption. With very few exceptions, experts have concluded that differences of less than 20% in the mean AUC between brand name and generic copies are acceptable. In general, differences in the clinical responses to drugs would not be



Observed differences in mean areas under drug concentration–time curve (AUCs) between generic and brand name products in 224 bioequivalence studies.

expected to be significant, or even evident, from differences of less than 20%. Therefore, the FDA established review procedures designed to assure with a high level of confidence that the mean AUCs of the brand name and generic products do not differ by more than 20%.

In fact, differences between brand name and generic products actually observed in bioequivalence studies submitted to the agency are small. In in vivo studies in ANDAs submitted under the provisions of the new law, the FDA has found that the average difference between the observed mean AUCs of the brand name and generic drug products is about 3.5%. For all generic drug products first eligible for FDA approval in an ANDA under the provisions of the 1984 law and approved during the first two years after enactment, the Figure shows the distribution of observed differences in mean AUCs between those products and their brand name counterparts. About 80% of these differences in means range between ±5%. Such differences are very small when compared with other variables of clinical therapeutic use and drug product quality and would not realistically produce clinically observed differences. As an example of drug product quality variability, the *United States Pharmacopeia* (the official compendium of drug standards) generally requires that drugs not differ from stated potency by more than ±10% and that drug potency not vary among dosage units by more than ±15%.

Although the extent of absorption, as measured by the AUC, is of primary importance, the FDA must also determine that the rates of absorption of the brand name and generic products are similar. The C_{max} and T_{max} parameters are used to determine the rate of absorption. Because these parameters are experimentally less precise and are of less therapeutic significance than the AUC, the agency uses a somewhat less rigid standard for them. While C_{max} values for the products are expected to fall within the same ±20% limits as the AUCs, if differences in C_{max} greater than 20% are encountered, a medical evaluation is made to determine whether the difference could be expected to have therapeutic significance. However, it should be noted that a lack of therapeutic significance is not the only basis for evaluating C_{max} comparability. If the C_{max} values differ to a greater extent, for example, ±30%, the application will rarely be approved, regardless of the therapeutic significance of such differences. The T_{max} parameter is used mainly as a qualitative check on the rate. While it may be of some significance in controlled-release products, it is rarely, if ever, pivotal in a bioequivalence determination.

Another criterion that has been used by the FDA, the "75/75 rule," is really a ratio analysis rather than a rigorous scientific or statistical test. Its use has declined in recent years, and it no longer serves as a basis for approving as bioequivalent a product that fails other criteria. The ratio analysis compares the plasma level from the generic product with that from the brand name product in each subject in the crossover study. The 75/75 rule derived its name from the requirement that the ratio be between 0.75 and 1.25 in at least 75% of the subjects tested. Although it has no statistical underpinning, the test does provide a measure of the intrasubject variability of products. For that reason, it is still useful.

The in vivo testing used to establish bioequivalence of generic drug products usually requires testing in only 20 or 30 healthy volunteers. In contrast, to demonstrate safety and efficacy, the FDA usually requires pioneer drug manufacturers to study the drug product in several hundred to a few thousand patients, because little is known about the new active drug ingredient's safety and effectiveness. There is a sound scientific rationale for this difference in the scope of information needed to gain marketing approval. Demonstrating that an active ingredient is safe and effective in a specific disease or condition, showing its mechanism of action, developing adequate labeling to describe its precise indications, determining appropriate dosage levels, and identifying side effects require investigations in a large number of patients. Once conditions for use for the active ingredient have been established, under the terms of the law, the FDA need ensure only that others wanting to market the same drug make their products correctly and that the products are in fact bioequivalent. This does not require duplicative testing in large numbers of patients, because showing statistically that one drug product can deliver the same plasma level as another requires far fewer human subjects.

Other Bioequivalence Considerations.—Three additional observations about bioequivalence are worthy of note.

First, the formulation on which a pioneer company conducts clinical testing is often not the same formulation that is ultimately approved for marketing. To relate its original formulation to the one intended for marketing, the pioneer company must perform the same kind of bioequivalence test on its own product that a generic manufacturer must perform later to relate its product to the brand name product.

Second, despite the existence of several well-known, documented cases of bioinequivalence among products that have not undergone the FDA's approval process, there is as yet no documented evidence of bioinequivalence involving a generic drug product approved by the FDA and evaluated as bioequivalent. Publicized cases of alleged bioinequivalence either have not been substantiated by the FDA on investigation or have involved drug products that have

not been approved by the FDA and evaluated as bioequivalent (eg, digoxin, a well-known documented problem with a drug that was marketed before the requirement for formal FDA premarketing review).

Finally, bioequivalence testing based on pharmacokinetic principles is a comparatively new and evolving science. Consequently, the current methodology employed in the design and evaluation of bioequivalence trials can be expected to continue to improve, as has been the case with safety and effectiveness trials. The FDA makes every effort to keep its procedures current with "state-of-the-art" technology and knowledge. To that end, the FDA recently conducted a three-day public hearing to discuss issues related to the bioequivalence of conventional-release, solid, oral-dosage form drugs.

Therapeutic Equivalence List

Since 1980, the FDA has published annually, with monthly updates, a listing entitled *Approved Drug Products With Therapeutic Equivalence Evaluations* (the *List*).[4] This is sometimes called the "Orange Book." The *List* was originally developed to facilitate decisions by states and private purchasers of drugs regarding the appropriateness of substitution of available multisource drug products. It is disseminated to all states by the FDA and is used by many states in their product selection determinations and formulary development. The *List* currently contains over 8000 approved prescription drug products. Of these, about 6000 are available from more than one manufacturer. Of these 6000 multisource drugs, about 5000, or more than 80%, have been evaluated as therapeutically equivalent by the FDA and are so designated in that publication. It should be noted that the percentage of drug products not evaluated as therapeutically equivalent is shrinking, principally because the 1984 law requires a showing of bioequivalence as a precondition of approval of generic drug products.

CONSIDERATIONS WHEN PRESCRIBING

There is universal agreement that not all generic drug products are therapeutically equivalent to their brand name counterparts. The FDA has evaluated fewer than 20% of the multisource drug products that appear in the *List* as lacking evidence of therapeutic equivalence with other brands of the same drug. The specific situation for each drug product is identified through a coding system in the *List*. An FDA evaluation of "not therapeutically equivalent" does not necessarily mean that the agency knows that the products are inequivalent. Rather, in most cases, it means that the agency does not have sufficient evidence that they are equivalent.

Federal law prohibits the inclusion of the product interchangeability code on the label, but publications detailing such information are routinely available through some state organizations. Furthermore, anyone can purchase the FDA's *List*, and the FDA is considering possible approaches to making the *List* available on-line by computer, for example, through its Electronic Bulletin Board. A magnetic tape containing the complete *List* is currently available from the National Technical Information Service on a quarterly basis by subscription.

Care must be exercised in using the *List*. Evaluations of therapeutic equivalence for prescription drug products are based on scientific evaluations by the FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of the FDA, to have an equivalent therapeutic effect and no greater potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as color, flavor, shape, packaging, preservatives, expiration date, and, in some instances, labeling. Further, a few differ in dosing schedules. In this case, bioequivalence means that the different brands produce equivalent blood levels when each is taken in accordance with its labeling ("package insert"). If products are substituted for each other, certain patients may be confused by differences in color or shape of tablets. This may require explanation to the patient. Different flavors may make a product more or less acceptable to an individual patient. Possible allergic reactions to a coloring or a preservative ingredient are additional considerations in prescribing and product selection. In addition, pharmacists must be familiar with the expiration dates and labeling conditions for storage of reconstituted products to assure that patients are properly advised when one such product is substituted for another. When such characteristics of a specific product are important in the treatment of a particular patient, a physician can always specify that a particular manufacturer's product be dispensed.

The FDA evaluates as therapeutically equivalent only those products that have the same active ingredients, dosage forms, and strengths and have been determined by the FDA to be bioequivalent (and are designated as equivalent in the *List*). There are a minority of approved drug products, both brand name and generic, that are not designated as therapeutically equivalent. However, these drug products, all cited with the appropriate code in the *List*, have been approved by the FDA. Therefore, these drug products were required to meet all standards for chemistry, manufacturing, and controls, and, in virtually all cases, each batch is required to be tested for dissolution before it can be released. While dissolution testing is not an absolute assurance of bioavailability, such testing greatly reduces the chance a product will not be absorbed. However, whether using brand name or generic drug products,

Excerpts From State Drug Product Selection Laws*

State	Type of Law†	Formulary
Alabama	P	None
Alaska	P	None
Arizona	P	None
Arkansas	P	Negative
California	P	Negative
Colorado	P	None
Connecticut	P	None
Delaware	P	Positive‡
District of Columbia	P	Positive
Florida	M	Negative
Georgia	P	None
Hawaii	M	Positive‡
Idaho	P	None
Illinois	P	Positive
Indiana	P	None
Iowa	P	None
Kansas	P	None
Kentucky	N	Negative‡
Louisiana	P	None
Maine	P	None
Maryland	P	Positive
Massachusetts	M	Positive
Michigan	P	None
Minnesota	P	None
Mississippi	M	None
Missouri	P	Negative
Montana	P	None
Nebraska	P	Negative
Nevada	P	Positive‡
New Hampshire	P	Positive‡
New Jersey	M	Positive
New Mexico	P	Positive‡
New York	M	Positive
North Carolina	P	None
North Dakota	P	None
Ohio	P	Positive
Oklahoma	P	None
Oregon	P	None
Pennsylvania	M	Positive
Puerto Rico	P	Positive
Rhode Island	M	Negative
South Carolina	P	None
South Dakota	P	None
Tennessee	P	Positive
Texas	P	None
Utah	P	Positive‡
Vermont	M	Positive
Virginia	P	Positive
Washington	M	Positive‡
West Virginia	N	Negative
Wisconsin	P	Positive‡
Wyoming	P	None

*From the NABP—*Survey of Pharmacy Law 1985-1986*, pp 30-31.

†P indicates permissive, ie, pharmacist may substitute if authorized by physician; M, mandatory, ie, pharmacists must substitute if authorized by physician.

‡Uses the Food and Drug Administration's *Therapeutic Equivalence List*.[4]

§The 1981 Oklahoma statute simply states that it is unlawful for a pharmacist to substitute without the authority of the prescriber or purchaser.

prescribers and pharmacists should always be mindful of the possibility of a drug product not being effective in every patient to whom it is administered.[3]

ACTIVITIES AT THE STATE LEVEL

All 50 states have now repealed the antisubstitution laws enacted in the 1940s and 1950s that prohibited alternative dispensing of prescription drug products. Approaches to generic substitution, called drug product selection in all of the state statutes, vary from state to state. No state, however, takes away from the physician the prerogative to limit or prohibit drug product selection. The Table characterizes each state's approach to product selection. Some states employ a positive formulary, which lists all of the drug products for which substitution is deemed appropriate. It may list drugs by active ingredient or by specific product. Other states employ a negative formulary system: a drug product may be substituted unless it appears on the formulary, which lists the drugs or drug products that the state has designated as inappropriate for substitution.

Some states allow substitution of drug products the FDA does not list as therapeutically equivalent; conversely, some states do not allow substitution of drug products that the FDA does list as therapeutically equivalent. About half the states do not use the formulary approach, but instead delegate to the prescribing physician and the pharmacist the determination of whether substitution is appropriate in any particular case. Although the FDA's *List* is only advisory, the *List* is, nonetheless, used as the formulary in at least nine of the 50 states and the District of Columbia. Some states have an independent process for determining formulary entries. In all cases, the final governmental decision as to which drug products may be substituted is a matter of states' prerogative.

In addition to generic substitution, some states are considering other types of substitution, ie, the dispensing of pharmaceutical alternatives (eg, the substitution of propoxyphene hydrochloride for propoxyphene napsylate) or the dispensing of therapeutic alternatives (eg, the substitution of metoprolol for propranolol). State proposals and bills for these nongeneric types of substitution have caused some confusion with generic substitution. In these states, concerns have been raised about either the interchangeability of products as they relate to therapeutically inequivalent products or the appropriateness of pharmacists making the kinds of determinations encompassed in concepts such as substitution of pharmaceutical or therapeutic alternatives. These nongeneric types of substitution are entirely within the domain of the states and are regulated as part of the practice of pharmacy and medicine.

CONCLUSION

The 1984 law and the FDA's generic drug policies are designed to approve for marketing high-quality generic drug products that are therapeutically equivalent to their brand name counterparts. Under the 1984 law, FDA approval of generic drug products eliminates the need for duplicative safety and efficacy tests, but requires bioequivalence testing to assure that generic products achieve plasma levels of the active ingredient comparable to those of their pioneer counterparts. In addition, all generic drugs must meet the same rigid FDA standards for manufacture and quality as do pioneer drugs.

As for substitution between generic products and their pioneer counterparts, there are situations in which even therapeutically equivalent drugs may not be equally suited for a particular patient. However, because of the rigor of the FDA approval process for both generic and brand name drug products, the FDA believes that health professionals can substitute drug products evaluated as therapeutically equivalent with the full expectation that patients will receive products of equal safety and effectiveness. Information as to the therapeutic equivalence of specific drug products, which is published and updated regularly by the FDA in the *List*, is available to physicians, pharmacists, and the general public.

The authors would like to thank the following persons for their advice and assistance in the preparation of the manuscript: Edwin V. Dunn, Jr, JD, Donald B. Hare, Peter H. Rheinstein, MD, JD, MS, and Frank J. Sasinowski, JD.

The *Approved Drug Products With Therapeutic Equivalence Evaluations*[4] is available from the Government Printing Office (GPO Order No. 917-001-00000); (202) 783-3238.

References

1. Pub L 98-417, 98 Stat 1585 21 USC §355 (1984).
2. Masson A, Steiner R: *Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws* Federal Trade Commission, 1985.
3. Crossen D: What's happening to pricing's marketing clout? *Pharmaceutical Executive* 1986;6(3):54-58.
4. *Approved Drug Products With Therapeutic Equivalence Evaluations*, ed 7. Rockville, Md, Food and Drug Administration, 1987.
5. Shular J: Gerry Mossinghoff. *Pharmaceutical Executive* 1986;6(2):36-40.
6. Hass AS, Morrison JC: *An Analysis of Prescription Drug Recall Rates*. OPE study 52. Rockville, Md, Food and Drug Administration, 1980.
7. Generic drugs. *Med Lett Drugs Ther* 1986; 28(704):1-2.

TITTAI P.06

Attachment C

Vol. 282 No. 21, December 1, 1999 From the Food and Drug Administration

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Author Information

Review of Generic Bioequivalence Studies

Jane E. Henney, MD

Questions have been raised recently about the ethics, safety, and effectiveness of generic substitutes for brand-name products. To address this issue, the FDA has examined all 127 in vivo bioequivalence studies in the 273 generic drug applications approved in 1997. The examinations focused on data that are used to evaluate the therapeutic equivalence of a generic and innovator drug.

Three measures were reviewed: the area under the plasma drug concentration–time curve from time 0 to time t (AUC [0-t]), the AUC from time 0 to infinity (AUC [0-Inf]), and the highest drug concentration (Cmax). The observed mean difference between the innovator's product and the generic product for AUC (0-t) was 3.47% (SD, 2.84), for AUC (0-Inf) it was 3.25% (SD, 2.97), and for Cmax it was 4.29% (SD, 3.72).

These findings confirm the results of a similar FDA review of 224 in vivo studies in applications for generic drug products that were approved in 1984 though 1986. In these studies, the average difference between the observed mean AUCs of the brand-name drug and the generic drug was about 3.5%.

Based on these results, practitioners and the public may be assured that if the FDA declares a generic drug to be therapeutically equivalent to an innovator drug, the two products will provide the same intended clinical effect.

AUTHOR INFORMATION

Jane E. Henney, MD
Commissioner of Food and Drugs

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Attachment D

Research-Based Pharmaceutical Research & Development (R&D) Expenditures Versus Marketing

Sources:
- Marketing data: IMS HEALTH, Inc., Plymouth Meeting, Pennsylvania.
- R&D data: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 2000, as published in the *Pharmaceutical Industry Profile 2000: Research for the Millennium*. Washington, D.C., 2000.

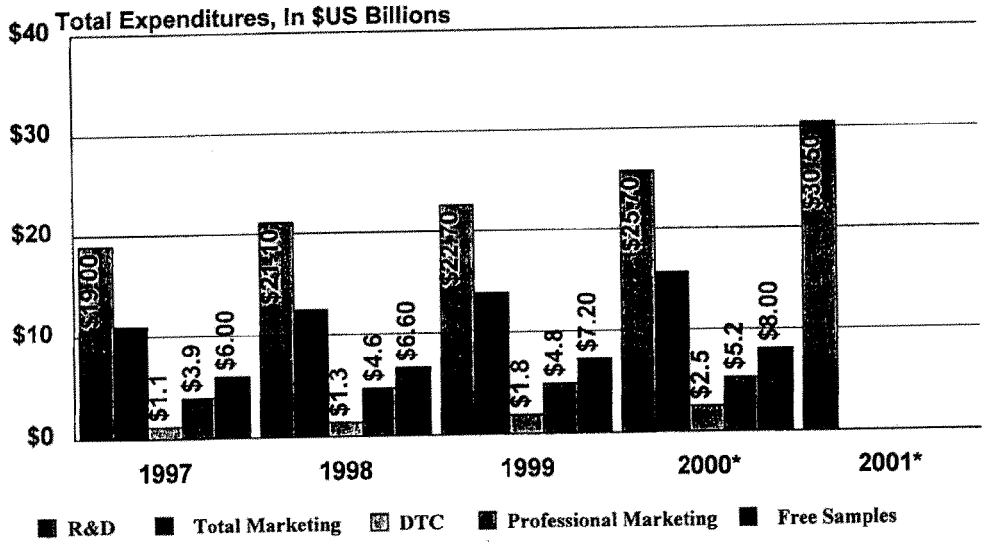
Note: All expenditures below are in billions of dollars

Year	R&D expenditures	Total marketing expenditures	Direct-to-consumer marketing expenditures	Professional marketing expenditures	Professional marketing expenditures *minus* samples
1996	$16.9	$9.2	$0.8	$8.4	$3.5
1997	$19.0	$11.0	$1.1	$9.9	$3.9
1998	$21.1	$12.5	$1.3	$11.2	$4.6
1999	$22.7	$13.9	$1.8	$12.0	$4.8
2000*	$25.7	$15.7	$2.5	$13.2	$5.2
2001*	$30.5				

*estimate

For further information, please see the attached graph.

In 2000, Research-Based Pharmaceutical Industry R&D Exceeded Marketing Dollars by 40 Percent

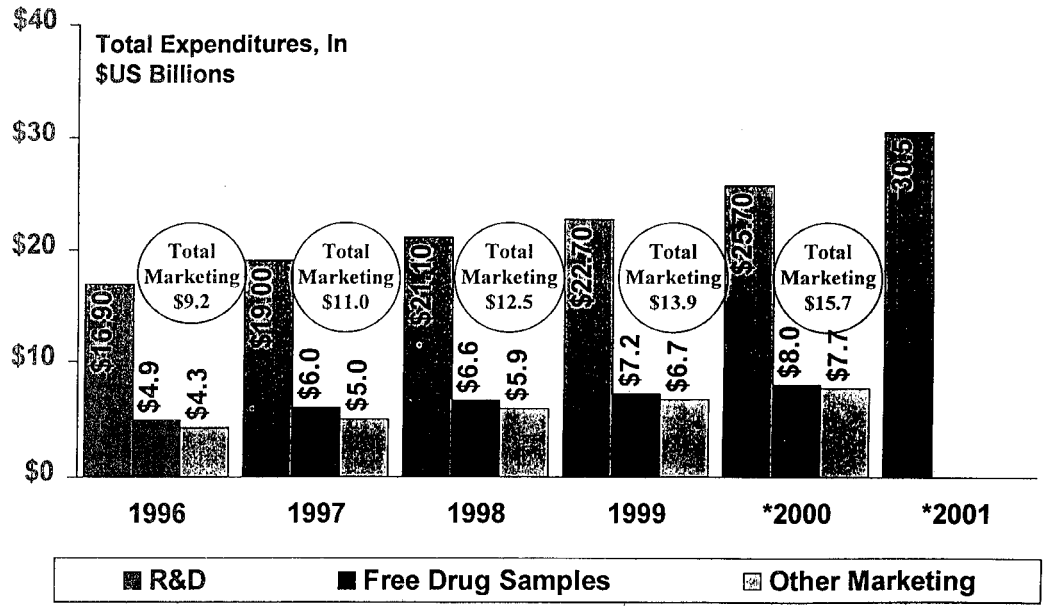


*R&D estimated expenditures **Numbers many not add exactly due to rounding

Sources: IMS HEALTH Inc., 2000, and Pharmaceutical Research and Manufacturers of America, 2001. Data from Annual Member Survey. (Note: Marketing data tabulated by IMS Health.)

Attachment E

Research-Based Pharmaceutical Industry R&D Spending Far Exceeds Marketing Expenditures



* Estimates

Sources: IMS HEALTH Inc., 2000, and Pharmaceutical Research and Manufacturers of America, 2001. Data from Annual Member Survey. (Note: Marketing data tabulated by IMS Health.)

Attachment F

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Ms. Kristy Gillis
The Committee on Energy and Health
The Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

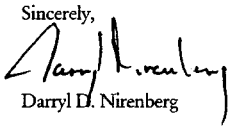
Dear Ms. Gillis:

We represent the Freedom to Advertise Coalition, a coalition of advertising and media associations committed to preserving the constitutionally protected right to advertise and promote legal products and services. Members of the Coalition include the American Association of Advertising Agencies, the American Advertising Federation, the Association of National Advertisers, the Direct Marketing Association, the Magazine Publishers of America, the Outdoor Advertising Association of American, and the Point of Purchase Advertising Institute.

On behalf of the Coalition, please allow us to submit the enclosed comments in response to testimony presented during the Subcommittee's June 13, 2001 hearing on "Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals."

We would be grateful if the enclosed comments could be included in the record of the June 13, 2001, hearing. Please let me know if there are any questions. We appreciate your time and attention to this matter.

Sincerely,



Darryl D. Nirenberg

Enclosure

COMMENTS of the FREEDOM TO ADVERTISE COALITION

In testimony before the Health Subcommittee of the House Committee on Energy and Commerce on June 13, 2001, Dr. John Golenski of RxHealth Value asserted that risk information, in his opinion, is not adequately or effectively conveyed to consumers in DTC advertising of prescription drugs. He recommended that Congress direct FDA to: (1) convene a task force of key stakeholders (including pharmaceutical manufacturers who advertise prescription drugs, as well as consumer groups, patient organizations, provider groups, payers and relevant experts) to develop and test new standards for information disclosure in Direct to Consumer ("DTC") advertising; (2) redefine the concrete meaning of "fair balance" in disclosing benefits and risks of advertised medications to include disclosure of other appropriate therapies in addition to alternative medications; and (3) further define "fair balance" to require disclosure of risks and side effects be given equal print and air time as the description of benefits in the same communication.

The assumptions and facts upon which Dr. Golenski bases these recommendations are incomplete and inaccurate. As a result, the recommendations, if implemented, would at best be ineffective and could serve to undermine the demonstrated benefits to consumers of DTC advertising of prescription drugs.

Communication of Risk Information

DTC advertising improves consumer knowledge about drugs, encourages consumers to seek medical attention, allows consumers to play a more active role in their own health care, educates consumers on how to recognize untreated diseases, and improves communication between patients and physicians. Despite these benefits, Dr. Golenski contends that risk information is not adequately communicated in DTC advertisement. The record on DTC advertisements, however, does not support this assertion and in fact, contradicts Dr. Golenski's contention that including more risk information in DTC advertisements would benefit consumers.

In response to the confusion that resulted from the previous approach to providing information on risks to consumers, FDA issued, in 1997, draft guidelines on broadcast advertising requirements.[1] Prior to this guidance, FDA required that a "brief summary" of prescribing information be included in all advertising, including broadcast advertising. The "brief summary" was intended for physicians for use in describing appropriate use of the drug. These "summaries" utilized technical terminology and proved to be quite lengthy and confusing to consumers, and ineffective in communicating the drug's risks.

Consequently, under the draft guidance, FDA eliminated the requirement of including the lengthy "brief summary" material regarding a drug's side effect. Instead, the guidance (which was finalized in 1999) required advertisements to list major health risks and side effects and also provide consumers with several means of obtaining the entire approved labeling (a toll-free mechanism, a web site address, a concurrently running print advertisement, and health care professionals).

- **Demonstrated Effectiveness of Risk Communication**

FDA surveys on DTC promotion have demonstrated that patients are utilizing the sources referenced in broadcast advertisements to obtain additional information on prescription pharmaceuticals. Private surveys confirm the FDA's findings.

FDA's 1999 telephone survey demonstrated that over 80% of patients notice the information in DTC advertisements for prescription drugs on risks or side effects of the drug as well as who should not take the drug.[2] The survey also showed that 10-20% of the patients sought additional information from toll-free telephone numbers, web sites, and print advertisements referenced in the broadcast advertisements – giving patients access to product labeling and full and detailed information regarding product risks.[3]

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[1] Draft Guidance for Industry - Consumer-Directed Broadcast Advertisements (July 1, 1997).
[2] Office of Medical Policy, Division of Drug Marketing, Advertising, and Communication, "Attitudes and Behaviors Associated with Direct-to-Consumer Promotion of Prescription Drugs," Main Survey Results.
[3] Statement by Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration, for the Hearing on "Recent Developments Which May Impact Consumer Access to, and Demand For, Pharmaceuticals," Before the Subcommittee on Health, House Committee on Energy and Commerce, June 13, 2001, p. 20.

In addition, FDA's comprehensive survey, which is consistent with other national surveys, showed that DTC advertisements led a substantial majority of respondents to initiate discussions with their doctors about a drug or a medical condition.[4] This is an encouraging finding, inasmuch as physicians are in the best position to describe a drug's associated risks as well as the appropriateness of the drug for their patients. The survey also revealed that physicians are fulfilling their role as "gate keeper" with respect to patient access to pharmaceuticals as only a small percentage of patients who asked their doctor about a prescription drug said that their doctor prescribed them the medication discussed. A majority of doctors informed their patients as to why they refused to prescribe the requested drug. Among the rationales given by physicians to their patients in such instances were: (1) that the drug was not right for the patient; (2) that the doctor preferred that the patient take a different drug; (3) that the drug had side effects of which the patient was not aware; (4) that the patient did not have the condition intended to be treated by the drug; (5) that a less expensive drug was available; (5) that there was no need for medication; or (6) that the patient's condition could be treated with an over-the-counter drug.[5]

- **FDA's Authority to Address Inadequate Risk Communication**

FDA has monitored closely DTC advertising to ensure that the "fair balance" requirement is met by inclusion in such advertising of proper risk information. As FDA points out, "product sponsors of prescription advertisements are required to submit their promotional materials to FDA around the time these materials are initially put into public use."[6] Thus, the Agency has an opportunity to review promotional materials for prescription drug advertisements when the materials are first disseminated to ensure that the advertisements fairly balance risk and benefit information. Furthermore, the majority of product sponsors also submit draft materials to FDA for review and comment on a routine basis, even though this is not required.[7]

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[4] Statement by Janet Woodcock, June 13, 2001, p. 20-21.
[5] "Attitudes and Behaviors Associated with Direct-to-Consumer Promotion of Prescription Drugs," Main Survey Results.
[6] Statement by Janet Woodcock, June 13, 2001, p. 17.
[7] Id.

In addition to reviewing and commenting on advertisements for prescription drugs prior to their dissemination, FDA also takes enforcement action against advertisements that may not adequately communicate the risks of the product.

A Task Force is Unnecessary

Dr. Golenski recommends that Congress direct FDA to convene a task force of key stakeholders to develop and test standards for information disclosure in DTC advertising. Such a task force is not necessary to give each of the groups listed by Dr. Golenski (pharmaceutical manufacturers who advertise prescription drugs, as well as consumer groups, patient organizations, provider groups, payers and relevant experts) the ability to comment to FDA on disclosure of information in DTC advertising. When FDA issued its draft guidance on consumer-directed broadcast advertisements in 1997, the Agency issued the draft document solely for comment purposes, inviting comments and suggestions. In addition, when FDA finalized the guidance in 1999, it encouraged sponsors and other interested parties to share research relating to the overall effects of DTC promotion on the public health. FDA has made it clear that it is open to any and all research and other information relating to DTC advertising.

Furthermore, the evidence of efforts by FDA, along with private groups, including TIME Inc., the National Consumers League, and the AARP, to study the impact of DTC advertising on consumers eliminates the need to establish a task force to conduct similar work. Such a task force is likely to be costly and redundant. Any and all of the pharmaceutical manufacturers, consumer groups, patient organizations, etc., are free to conduct testing on information disclosure, make the studies public, submit the studies to FDA and request that FDA modify its policies regarding DTC advertising.

Changes to Current Fair Balance Requirements are Unnecessary

- **Disclosure of Other Therapies and Medications Impractical**

Dr. Golenski recommends that Congress direct FDA to redefine the meaning of "fair balance" in disclosing benefits and risks of advertised medications to include disclosure of other appropriate therapies in addition to alternative medications. This recommendation is impractical and proposes

an inappropriate application of the term "fair balance." FDA's regulations require that prescription drug advertising contain a true statement relating to side effects, presenting a fair balance between information relating to side effects and contraindications and information relating to the effectiveness of the drug.[8] The purpose of the fair balance requirement is to ensure that consumers are presented with adequate information regarding a particular product's risks and benefits. Advertising available alternative therapies or medications is outside the scope of expertise and knowledge of a manufacturer of a particular drug. While a drug manufacturer is required to have extensive information about the risks and benefits associated with a drug that it produces, it would impose an unreasonable burden on a drug manufacturer to require that it have detailed knowledge about, and spend its advertising resources on, promoting other drugs or therapies.

Requiring that a drug manufacturer advertise other drugs and therapies could raise number of complex issues, including (1) the First Amendment rights of the advertiser, (2) the rights of the manufacturers of the other drugs that might be named in a competitor's advertisement; and (3) how to determine what qualifies as an "alternative" to a particular drug. Compelling a manufacturer to essentially advertise a competing product gives the competitor an enormous competitive advantage, at the cost of the advertising manufacturer. A manufacturer of an "alternative" drug product might not wish to have the name of its drug associated with its competitors and could object to having its drug named in its competitor's advertisement.

Further, one would have to wonder which drugs would be considered "alternatives" and who would make this decision. The scope of what constitutes an "alternative" drug would require determinations on whether to include all generic versions of the drug, all drugs in a class, only other drugs in the same form (i.e., tablet or capsule), or with the same dosage, or side effects, or patient population. Identifying alternative therapies would be even more problematic and would require consideration of whether to include non-traditional therapies or even common off-label use.

Fair Balance Already Requires Balance of Risks and Benefits

Dr. Golenski's recommendation that "fair balance" be further defined to require disclosure of risks and side effects be given equal print and air time as the description of benefits in the same

[8] 21 C.F.R. § 202.1(e)(5).

communication is unnecessary – especially given the current regulation of prescription drug advertising. The purpose of this recommendation has already been achieved– FDA's survey demonstrated that virtually as many consumers (87%) recalled seeing DTC advertisements that contained information about benefits of the drug as did seeing risk or side effects (82%). As noted previously, FDA rejected the previous approach of providing extremely detailed risk and side effect information as too confusing, complicated, and therefore, counterproductive for consumers.

***

WELLPOINT
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VIA FEDERAL EXPRESS

August 1, 2001

The Honorable Michael Bilirakis
Chairman
Subcommittee on Health
U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

Dear Mr. Chairman:

This is in response to your letter of July 19, 2001 setting forth certain questions in response to my testimony on "Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals" before your Subcommittee on June 13, 2001. The questions you have posed, together with the answers which are respectfully submitted on behalf of WellPoint Health Networks Inc. ("WellPoint"), are set forth below.

Question 1: "You note in your testimony that Section 503(b)(3) allows for a switch from prescription status to OTC status, but wasn't this provision passed 50 years ago as a way for FDA to harmonize the treatment of drugs with the same active ingredients but which were being sold both prescription and OTC? How then can it be used to do switches over the objection of the manufacturer?"

Answer to Question 1: One of the purposes behind the 1951 Durham-Humphrey Amendment ("DH Amendment") to the Federal Food, Drug, and Cosmetic Act ("FDCA") was to harmonize the treatment of drug products with the same active ingredient, some of which were sold both by prescription ("Rx") and over-the-counter ("OTC"). However, plainly read, Section 503(b)(3) states that FDA possesses the authority to effectuate a switch from Rx to OTC regardless of the consent of the manufacturer. It states:

> [FDA] may by regulation remove drugs subject to section 505 [i.e., NDAs] from the requirements of paragraph (1) of this subsection [the prescription labeling exemption] when such requirements are not necessary for the protection of the public health.

See 21 U.S.C. § 503(b)(3). Furthermore, the legislative history of the DH Amendment indicates that the Amendment had dual purposes: (1) to protect the public from abuses in the sale of potent prescription drugs; and (2) to relieve pharmacists and the public from unnecessary restrictions on the dispensing of drugs that are safe for use without the supervision of a physician. See Sen. R. No. 946 at 1, reprinted in 1951 U.S.C.C.A.N. 2454. Viewed in combination, it is clear that FDA is to make the determination whether the prescription labeling exemption is necessary for the protection of public health, and where it is not, the unnecessary restrictions should be removed. Neither the statute nor the legislative history gives any credence to the idea that it is the manufacturer and not FDA who should be making this important safety determination.

In the case of antihistamine drug products, it is clear that these products are safe for OTC use. For over 15 years there has been a final OTC monograph for antihistamine drug products. See 21 C.F.R. Part 341. This monograph went through an extensive notice and comment rulemaking and there is an extensive record of consumers being able to self-diagnose and self-treat the symptoms of allergic rhinitis (runny nose, itchy, watery eyes). Furthermore, the manufacturers of these second generation antihistamines have gone to great lengths to advertise that their products are as safe or even safer than products currently marketed under this monograph and in some instances have even compared the safety of their products to placebos and/or "sugar pills." This is consistent with the fact that in many countries around the world, including Canada and Australia, these products are already available to consumers OTC, and just last month the United Kingdom Medicines Control Agency announced it would switch Claritin® (Schering-Plough) and Zyrtec® (marketed by UCB Pharma in the U.K.) to unrestricted OTC status. See The Tan Sheet dated July 2, 2001 and Medicines Control Agency Consultation Letter MLX 272 (copies attached).

Wellpoint firmly believes that these products are safe for OTC use, a determination that was overwhelmingly endorsed on May 11, 2001 by the FDA's advisory committee which examined this issue. WellPoint believes that these products should be switched to OTC status. Wellpoint acknowledges, however, that it is FDA, and FDA alone, that is empowered to make the final determination on this issue and all other issues of the safety and effectiveness of drug products.

Question 2: "Are you aware of any instance in which FDA used Section 503(b)(3) to move a drug from prescription to OTC status over the objection of a manufacturer?"

Answer to Question 2: No, we are not aware of any instance in which FDA used Section 503(b)(3) to move a drug from prescription to OTC status over the objection of a manufacturer. We do believe, however, that it is FDA's sole responsibility and charge under the FDCA to determine whether drugs are safe and effective for use without a prescription. In this particular instance, we believe that FDA should find these second generation antihistamines safe and

effective for OTC use and thus remove the prescription labeling requirement from the labeling, whether or not the manufacturers are in favor of the switch.

Question 3: "To be sold OTC, a drug must be safe; a consumer must be able to self-diagnose; and the label must be comprehensible to the consumer. If the FDA is allowed to do switches over the objections of manufacturers, who would perform label comprehension studies?"

Answer to Question 3: In the case of second generation antihistamines, FDA has already made the determination that label comprehension studies are not required for approval. Although, in many instances, label comprehension studies are essential to approval and would most appropriately be conducted by the manufacturer, in this case there is already a final monograph which includes required labeling instructions that has been in place for over 15 years. In the case of antihistamines (both those covered by the OTC monograph and the second generation antihistamines), there is no question that consumers can self-diagnose, self-treat, and comprehend labeling instructions for these products. Wellpoint cannot comment on the appropriateness of other hypothetical OTC switches and whether label comprehension studies would or would not be required as a prerequisite of approval.

Question 4: "Are you in any way concerned that forced switches may impact the ability of pharmaceutical companies to innovate?"

Answer to Question 4: Wellpoint has petitioned FDA to switch second generation antihistamine drug products from Rx to OTC use because we believe that consumers can appropriately self-diagnose and self-treat with these products and that they are safe and effective for OTC use. Wellpoint does not believe that the OTC switch of second generation antihistamines would impact the ability of pharmaceutical companies to innovate. Wellpoint believes this proposed switch is a unique situation and cannot comment on the impact of other hypothetical switches that might be proposed in the future.

I appreciate having the opportunity to respond to your inquiry. If you have any further questions, please let me know at your earliest convenience.

Very truly yours,

Thomas C Geiser

Thomas C. Geiser

TCG:jmf

Source: All Sources > Area of Law - By Topic > Healthcare & Medical > Legal News > FDC Reports > FDC Reports Newsletters, Combined
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The Tan Sheet

Vol. 9; No. 27; Pg. 3

July 2, 2001

SECTION: THE NEWS THIS WEEK

LENGTH: 709 words

TITLE: CLARITIN, ZYRTEC "SUITABLE FOR GENERAL SALE" IN **UK**, MCA STATES

TEXT:
Claritin and Zyrtec are slated to switch to over-the-counter sale in the **UK** later this year following the June 15 publication of a Medicines Control Agency "consultation letter."

According to the Proprietary Association of Great Britain, a third party submitted the switch applications to MCA. Claritin marketer Schering-Plough said it plans to submit comments registering its objections to a **UK** switch. Zyrtec is marketed in the **UK** by UCB Pharma, which could not be reached for comment.

At a May 11 joint meeting of FDA's Nonprescription and Pulmonary-Allergy Drugs Advisory Committees convened to discuss whether Claritin (loratadine), Zyrtec (cetirizine) and Aventis' Allegra (fexofenadine) are clinically appropriate for OTC sale, Schering said it has opposed nonprescription sale of its antihistamine in every country where it has been proposed.

Schering, Aventis and Zyrtec's U.S. marketer Pfizer all contest switching the antihistamines in the U.S. ("The Tan Sheet" May 14, pp. 3-4 and May 21, pp. 12-15). The matter recently was taken up at a House Energy & Commerce/Health Subcommittee hearing ("The Tan Sheet" June 18, p. 3).

Claritin and Zyrtec have been available as "pharmacy" (P) status drugs in the **UK** since 1993, when they were downgraded from prescription-only medicine (POM) status. Currently, they can be obtained without a prescription but may only be dispensed in drugstores.

"General sales list" (GSL) status would permit Claritin and Zyrtec - and any future generic equivalents - to be distributed in non-pharmacy retail outlets such as supermarkets and mass merchandisers.

Full OTC status is granted when MCA deems a drug GSL at the recommendation of the Committee on the Safety of Medicines, a panel of outside experts similar to FDA's advisory committees.

According to British law, "a medicine can be classified as suitable for general sale if it can, with reasonable safety, be sold or supplied without the supervision of a pharmacist," the "consultation letter" says.

MCA notes both drugs present "no safety concerns with regard to diagnosis or misdiagnosis of

the condition, or precautions for use (interactions or side effects)."

The intended use for both drugs under GSL would be the same as their P indications. In the **UK**, Claritin and Zyrtec are indicated for "the symptomatic relief of perennial rhinitis, seasonal allergic rhinitis and idiopathic chronic uticaria in adults and children aged 12 years and over." The dosage would be 10 mg for both, and packaging restrictions would permit only seven tablets per container.

The letter lists four other drugs that have been recommended for a switch from P to GSL. Pediatric ibuprofen liquid preparations (100 mg/5 mL) would become available on GSL with a maximum dose of 200 mg - half the adult limit - and a maximum daily intake of 800 mg for children under 12.

A single package would be allowed to contain no more than 20 5 mL unit doses and the drug would carry indications for "rheumatic or muscular pain, headache, dental pain, feverishness or symptoms of colds and influenza."

An alternate form of non-steroidal anti-inflammatory drug ibuprofen lysine also is suggested as a P-to-GSL switch. The recommended dose would be 200 mg; the drug would come in packs of 16 tablets or fewer and be intended for people over age 12.

A children's liquid formulation of paracetamol (acetaminophen) is listed as appropriate for general sale as well. For children age six to 12, the drug would be restricted to a 5% concentration in unit doses of 5 mL and a maximum of 10 units per package. Current **UK** liquid paracetamol preparations are available in only 2.5% strength but may be sold in 160 mL containers; 2.4% strengths in 100 mL bottles are sold for children younger than 12.

The agency also recommends low-dose aspirin for heart attack and stroke prevention be available for general sale. MCA suggests permitting aspirin 75 mg for GSL sale in packs of 28; higher doses for pain relief may not be sold in the **UK** in larger than 16-count packages.

MCA will accept comments until Aug. 3 but expects to enact the changes by October. The agency estimates the cost for each manufacturer to change labeling for a switch would be [L] 5,000 (about $7,039).

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To Interested Organisations[1]

15 June 2001

Dear Sir or Madam

CONSULTATION LETTER MLX 272

Proposed amendments to:
THE MEDICINES (PRODUCTS OTHER THAN VETERINARY DRUGS) (GENERAL SALE LIST) ORDER 1984 (SI 1984/769) and
THE MEDICINES (SALE OR SUPPLY)(MISCELLANEOUS PROVISIONS) REGULATIONS 1980 (SI 1980/1923)

INTRODUCTION

1. I am writing to consult you, under section 129(6) of the Medicines Act 1968 ("the Act"), on proposed amendments to: The Medicines (Products Other Than Veterinary Drugs) (General Sale List) Order 1984 (SI 1984/769)[2] ("the GSL Order") and the Medicines (Sale or Supply) (Miscellaneous Provisions).Regulations 1980 (SI 1980/1923)[3] ("the Sale or Supply Regs").

BACKGROUND

2. Under Section 51 of the Act (see Appendix 1) a medicine can be classified as suitable for general sale if it can, with reasonable safety, be sold or supplied without the supervision of a pharmacist. The GSL Order, made under that section, lists medicines that can be made available on general sale. The Sale or Supply Regulations set out pack size limits for certain GSL medicines at section 8. The proposed amendments to the Order and Regulations are set out below.

PROPOSED AMENDMENTS TO THE GSL ORDER & SALE OR SUPPLY REGULATIONS

3. **two antihistamine substances - cetirizine dihydrochloride and loratadine**
Both substances have been available without prescription since 1993, with a maximum dose of 10mg, in packs of 10 tablets. They are used for the symptomatic relief of perennial rhinitis (persistent sneezing), seasonal allergic rhinitis (hayfever) and idiopathic chronic urticaria (itchy rashes) in adults and children aged 12 years and over. Both substances are classified as non-sedating antihistamines and there are no safety concerns with regard to diagnosis or misdiagnosis of the condition, or precautions for use (interactions or side-effects).

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[1] See Appendix 2
[2] The GSL Order has been amended by SIs 1985/1540, 1987/910, 1989/969, 1990/1129, 1992/1535, 1994/2410, 1995/3216, 1997/2043, 1998/2170, 1999/852, 1999/2535 and 2000/1092.
[3] The Sale or Supply Regs have been amended by SIs 1982/28,1990/1124, 1994/2411, 1995/3215, 1997/1831 & 2045, 1999/644 & 2510, 2000/1070 & 2494.

The Committee on Safety of Medicines (CSM) has advised that both cetirizine dihydrochloride and loratadine could safely be on general sale provided that:

- They are supplied in tablet form;
- They are for the symptomatic relief of perennial rhinitis, seasonal allergic rhinitis and idiopathic chronic urticaria in adults and children aged 12 years and over;
- The maximum strength is 10mg; and
- They are supplied in packs containing not more than 7 tablets.

We propose to amend the GSL Order and Sale or Supply Regulations accordingly.

4. **aspirin 75mg**

Low dose aspirin is used in the prevention of further heart attack or stroke. The Sale or Supply Regulations currently limit the maximum pack size of aspirin tablets or capsules on general sale to 16. The CSM has advised that enteric-coated aspirin 75mg may be on general sale in packs of up to 28 tablets (i.e. a month's supply). We propose to amend the Sale or Supply Regulations accordingly.

5. **ibuprofen (liquid preparations)**

Ibuprofen is currently available on general sale for use in adults and children over the age of 12 years. The maximum strength is 200mg, the maximum dose is 400mg and the maximum daily dose is 1200mg. It is to be used only for the treatment of rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, or symptoms of colds and influenza. It is available in the form of tablets, capsules, powder and granules, in a pack of no more than 16 tablets or capsules, or 12 sachets of powder or granules.

CSM has advised that a liquid preparation of ibuprofen 100mg/5ml for use in children under the age of 12 years could safely be made available on general sale provided
that:

- It is for internal use;
- It is for the treatment of rheumatic or muscular pain, headache, dental pain, feverishness, or symptoms of colds and influenza;
- The maximum dose is 200mg;
- The maximum daily dose is 800mg; and
- It is supplied in individual unit doses of not more than 5ml each, in a pack containing not more than 20 doses.

We propose to amend the GSL Order and Sale or Supply Regulations accordingly.

6. **ibuprofen lysine**

Ibuprofen lysine is a water-soluble salt of ibuprofen, a well-established analgesic, anti-inflammatory and antipyretic. It is more rapidly absorbed than ibuprofen but is used for the same indications. It has been available without prescription since 1996 and has been shown to be comparable to ibuprofen with respect to safety and efficacy.

CSM has advised that it would be safe to allow ibuprofen lysine to be available on general sale when it is used internally for the treatment of rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, or symptoms of colds and influenza, in adults and children over 12 years of age, when the maximum strength is equivalent to 200mg ibuprofen, the maximum dose is equivalent to 400mg ibuprofen, and the maximum daily dose is equivalent to 1200mg ibuprofen, and when it is supplied in a pack containing no

more than 16 tablets. We propose to amend the GSL Order and Sale or Supply Regulations accordingly.

7. **paracetamol (liquid preparations)**
Some liquid preparations of paracetamol are available on general sale. Preparations with a maximum strength of 2.5% are for use by adults and children aged 12 years and over and have a maximum pack size of 160ml, while preparations with a maximum strength of 2.4% are for use in children aged less than 12 years and must be presented in individual unit doses of not more than 5ml each, to a maximum of 20 unit doses.

Medicines Commission have advised that public consultation may take place on a proposal to amend the GSL Order and Sale or Supply Regulations to permit the general sale of 5% strength liquid preparations of paracetamol, under the following conditions:

- for use in children aged 6 to 12 years
- presented in unit doses of not more than 5ml, in packs of not more than 10 unit doses.

Medicines Commission have recommended that if the 5% preparations in unit doses become available on general sale, they should be in packaging that is sufficiently distinct from that of the lower strength (2.4%) preparations, to prevent confusion between the two.

8. **potassium chloride**
Potassium chloride is listed in both Table A (substances for internal and external use) and Table B (substances for external use only) of schedule 1 to the GSL Order. This duplication is confusing and we propose to remove the surplus entry in Table B and clarify the entry in Table A to specify both internal (maximum strength of 0.15% for treatment of acute diarrhoea) and external use.

9. **sodium fluoride**
Medicines containing sodium fluoride are used in the prevention of dental caries (tooth decay). Mouthwashes containing up to 0.2% sodium fluoride are available without a prescription but supply is restricted to pharmacies. However, the Cosmetic Products (Safety) Regulations permit the use of fluoride compounds in oral hygiene products up to a maximum total fluorine content of 0.15% fluorine (which is equivalent to 0.33% sodium fluoride). Toothpastes and mouthwashes containing sodium fluoride are marketed under these regulations and are freely available and there are no apparent safety issues.

We therefore propose to amend the GSL Order to permit the general sale of products containing sodium fluoride for use in the prevention of dental caries, in the form of daily-use mouthwashes with a maximum strength of 0.05% sodium fluoride, and mouthwashes for other than daily use with a maximum strength of 0.2%.

COMMENTS

10. You are invited to comment on these proposals and a form is attached for your reply.

11. You are also invited to comment on the possible impact on business of the proposed changes and draft Regulatory Impact Assessment which is attached.

Copies of the final version will be made available to Ministers, Parliament and to the public. It would therefore be helpful if you could identify and quantify any direct or indirect costs (recurring or non-recurring) or any profits which would be likely to arise for business in your sector if these changes are made.

12. Comments should be addressed to Tricia Griffiths, in room 14-110 at the above address, to arrive by **3 August 2001.**

13. The Medicines Commission will be asked to consider the proposals in the light of comments received and their advice will be conveyed to Ministers. Subject to the agreement of Ministers, we plan to implement the changes by Statutory Instrument coming into force in October 2001. This will be available from Stationary Office Books and may be viewed on their website http://www.hmso.gov.uk/stat.htm

MAKING COPIES OF REPLIES AVAILABLE TO THE PUBLIC

14. To help informed debate on the issues raised by this consultation exercise, and within the terms of the Code of Practice on Access to Government Information ("Open Government"), the Agency intends to make copies of replies received publicly available. Copies will be available shortly after the public consultation has ended.

15. The Agency's Information Centre at Market Towers will supply copies upon request. Copies may be further reproduced. An administrative charge, to cover the cost of photocopying and postage, may be applied. Alternatively, personal callers can inspect the replies at the Information Centre by prior appointment. To make an appointment, telephone 020 7273 0351.

16. It will be assumed that your reply can be made publicly available in this way unless you indicate that you wish all, or part of it, to be treated as confidential and excluded from this arrangement. Under the Code of Practice on Access to Government Information, the Agency will not release confidential replies or replies containing personal confidential information.

Yours faithfully,

JAMES COPPING
POST-LICENSING DIVISION
✉ 14-111 Market Towers

REGULATORY IMPACT ASSESSMENT

THE MEDICINES (PRODUCTS OTHER THAN VETERINARY DRUGS) (GENERAL SALE LIST) AMENDMENT ORDER 2001 and
THE MEDICINES (SALE OR SUPPLY)(MISCELLANEOUS PROVISIONS) AMENDMENT REGULATIONS 2001

1. PURPOSE AND INTENDED EFFECT OF THE MEASURES

The Issue

1.1 The Medicines Act 1968 requires all medicinal products to be licensed, to ensure that they are safe, effective and of good quality. It also sets out criteria for the control of their supply.

- Those which meet the criteria for prescription control are listed in The Prescription Only Medicines (Human Use) Order 1997, SI 1997/1830.
- Those which meet the criterion for general sale are listed in The Medicines (Products Other Than Veterinary Drugs)(General Sale List) Order 1984 SI 1984/769.

The criteria for classifying medicinal products are set out at Appendix 1.

1.2 Procedures for reclassification are published as MAL 77 and MAL 82, available from the MCA Information Centre, Market Towers, telephone 020 7273 0351. Following consultation with Trade and Professional Associations, Ministers have agreed that proposed amendments to these Orders should be considered twice yearly. Any changes are implemented by Statutory Instrument. These are available from Stationary Office Books and may be viewed on their website http://www.hmso.gov.uk/stat.htm

Objectives

1.3 These amendments are intended to allow medicines containing cetirizine, and loratadine (for relief of rhinitis and urticaria), ibuprofen lysine, liquid preparations of ibuprofen, and liquid preparations of paracetamol at the higher strength of 5%, and mouthwashes containing sodium fluoride (to prevent dental caries) to be on general sale. They would also allow medicines containing aspirin 75mg (for the prevention of further heart attack or stroke), which are already available on general sale, to be supplied in a larger pack.

2. BENEFITS IDENTIFIED AND QUANTIFIED

The additions to the General Sale List Order are being proposed largely at industry's request. They will benefit the public by making these medicines for common ailments more readily available.

3. COMPLIANCE COSTS FOR BUSINESS

3.1 **Business sector affected**

Manufacturers of medicinal products come under business sector 24421 (Manufacture of medicaments) *Business Monitor PA1003 - Size analysis of United Kingdom Business (1996).*

3.2 **Actual cost of the proposal on an annual basis**

The proposal would require an amended label and leaflet for each of these products which we estimate would cost £5,000. There are eight products involved, so the total initial cost of the proposal would be £40,000. These amendments have been proposed at the request of the manufacturers because general sale list status provides a wider market and the potential for greater sales.

It is therefore unlikely that they will pass this cost on to the public. We estimate that there will be no further cost arising from the proposal.

4. **RESULTS OF CONSULTATION**

Consultation letter MLX 272 will be sent to 162 interested organisations and to the companies involved. The trade associations (the Association of British Pharmaceutical Industry, and the Proprietary Association of Great Britain) copy it to their members. The letter will also be sent to all interested divisions of the Department of Health and to the Health Departments of the Scottish Executive, the National Assembly for Wales and the Northern Ireland Executive. Copies will be sent to the Veterinary Medicines Directorate, and to the Department of Agriculture in Northern Ireland. Comments are also invited on the likely impact on business costs of the proposed changes. We will allow six weeks for replies, with a deadline of 3 August 2001. Copies of the responses may be obtained from the Medicines Control Agency's Information Centre (phone 020 7273 0000) when the consultation is completed. The responses to consultation will be submitted to the Medicines Commission for advice.

5. **SUMMARY AND RECOMMENDATIONS**

We recommend that the GSL Order and the Sale or Supply Regulations be amended to allow medicines containing cetirizine, and loratadine (for relief of rhinitis and urticaria), ibuprofen lysine, liquid preparations of ibuprofen, liquid preparations of 5% paracetamol, and mouthwashes containing sodium fluoride to be on general sale; and medicines containing aspirin 75mg, already available on general sale, (for the prevention of further heart attack or stroke) to be supplied in a larger pack.

Contact point and date

For further information please contact:

Tricia Griffiths
POST-LICENSING DIVISION
Medicines Control Agency
✉ 14-110 Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ
☎ 020 7273 0366 020 7273 0293

27 June, 2001

Appendix 1

CRITERIA FOR CLASSIFYING MEDICINAL PRODUCTS

GENERAL SALE LIST

Section 51 of the Medicines Act 1968 provides that :

> **"Ministers may by order specify descriptions or classes of medicinal products, as being products which in their opinion can with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist."**

The 1967 White Paper *Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines (Cmnd 3395)* which preceded the introduction of the Medicines Bill into parliament contemplated that in the field of human medicines the General Sale List would comprise products "where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

The Medicines Commission's *Report on a General Sale List of Medicinal Products for Human Use*, published in April 1973, which advised Ministers on the introduction of the General Sales List, noted that they accepted this as an appropriate elaboration of the expression "with reasonable safety".

Appendix 2

MLX CONSULTATION LIST : MLX 272

Advertising Association
Advertising Standards Authority
Advisory Committee on Misuse of Drugs
Age Concern
All-Party Pharmacy Group
Arthritis Care
Association of Anaesthetists of Great Britain and Northern Ireland
Association of British Cardiac Nurses
Association of British Health Care Industries
Association of British Pharmaceutical Industries
Association of Community Health Councils of England & Wales
Association of Pharmaceutical Importers
Association of Surgeons of Great Britain and Ireland
Asthma & Allergy Research
British Association of Dermatologists
British Association of European Pharmaceutical Distributors
British Association of Pharmaceutical Physicians
British Association of Pharmaceutical Wholesalers
British Cardiac Patients Association
British Contact Dermatitis Group
British Dental Association
British Dental Association (Northern Ireland)
British Dental Association (Wales)
British Dental Trade Association
British Diabetic Association
British Epilepsy Association
British Generic Manufacturers Association
British Heart Foundation
British Institute of Regulatory Affairs
British Medical Association
British Medical Association (Northern Ireland)
British Medical Association (Scottish Branch)
British Medical Association (Welsh Office)
British Oncological Association
British Pharmacological Society
British Retail Consortium
British Society for Allergy and Clinical Immunology
British Society for Rheumatology
British Society of Gastroenterology
British Toxicology Society
Central Medical Advisory Committee
Chemist & Druggist
College of Health

College of Optometrists
College of Pharmacy Practice
Committee of Practitioners & Health Visitors Association (NI)
Community Pharmacy Magazine
Community Services Pharmacists Group
Company Chemist Association Ltd
Consolidated Communications
Consumers Association
Co-operative Pharmacy Technical Panel
CWS Ltd (Trade Liaison Department)
Department of Agriculture & Rural Development [N Ireland]
Department of Health, Social Services & Public Safety - Public Health Branch [N Ireland]
Dispensing Doctors Association
Doctor Magazine
Drug & Therapeutics Bulletin
Drug Information Pharmacists Group
English Board for Nursing, Midwifery & Health Visiting
European Association of Hospital Pharmacists
FDC Reports (Elsevier Science)
General Medical Council
General Medical Services Committee
General Medical Services Committee (Wales)
General Practitioners Association (NI)
Genetic Interest Group
Guild of Healthcare Pharmacists
Health & Safety Executive
Health Service Commissioner
Health Which?
Help the Aged
Home Office - Action Against Drugs Unit
Imperial Cancer Research Fund
IMS Health Division IDRAC
Independent Healthcare Association
Independent Television Commission
Insulin-Dependent Diabetics Trust
International Research Consultants
Joint Consultants Committee
Local Authority Central Office of Trading Standards (LACOTS)
Long-Term Medical Conditions Alliance
Medical Defence Union
Medical Protection Society Ltd
Medical Research Council
Medical Women's Federation
MIMS (Haymarket Medical Publishing Ltd)
National AIDS Trust
National Assembly for Wales, Health Department

National Association of GP Co-operatives
National Association of Women Pharmacists
National Back Pain Association
National Board for Nursing, Midwifery & Health Visiting (NI)
National Consumer Council
National Eczema Society
National Federation of Retail Newsagents
National Pharmaceutical Association
Neonatal and Paediatric Pharmacists Group
Neurological Alliance
NHS Information Authority (Coding & Classification)
Northern Ireland Consumer Council
Ophthalmic Group Committee
OTC Bulletin
OTC Business News (Informa Publishing Group Ltd)
OTC News & Market Report
Overseas Doctors Association in the UK Ltd
Paediatric Chief Pharmacists Group
Patients Association
Pharmaceutical Contractors Committee (Northern Ireland)
Pharmaceutical Journal
Pharmaceutical Services Negotiating Committee
Pharmaceutical Society for Northern Ireland
PharMAG
Prescription Pricing Authority
Proprietary Association of Great Britain
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Nursing (Northern Ireland)
Royal College of Nursing (Wales)
Royal College of Obstetricians & Gynaecologists
Royal College of Ophthalmologists
Royal College of Paediatricians and Child Health
Royal College of Pathologists
Royal College of Physicians & Surgeons (Glasgow)
Royal College of Physicians (Edinburgh)
Royal College of Physicians (London)
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons (Edinburgh)
Royal College of Surgeons (England)
Royal College of Surgeons (Faculty of Dental Surgery)
Royal Colleges of Physicians : Faculty of Pharmaceutical Medicine
Royal Colleges of Physicians : Faculty of Public Health Medicine
Royal Pharmaceutical Society of Great Britain

Royal Pharmaceutical Society of Great Britain (Scotland)
Royal Pharmaceutical Society of Great Britain (Welsh Executive)
Royal Society for the Promotion of Health
Scottish Consumer Council
Scottish Executive, Department of Health
Scottish General Medical Services Committee
Scottish Pharmaceutical General Council
Scottish Wholesale Druggists Association
Scrip Ltd
Social Audit Unit
Society of Pharmaceutical Medicine
St Andrew's Ambulance
St John Ambulance
St John Ambulance (NI)
Switch
Terrance Higgins Trust
Tic-Tac Administration
Tutsells Enterprise IG (The Brand Union Limited)
UK Committee for Nursing, Midwifery & Health Visiting
UK Clinical Pharmacy Association
UK Homoeopathic Medical Association
UK Inter-Professional Group
University of Aberdeen : Department of General Practice & Primary Care
Veterinary Medicines Directorate (VMD)
Welsh Consumer Council
Women in Medicine

To : Tricia Griffiths
Medicines Control Agency
Room 14-110 Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

From : _____
_____
_____
_____
_____

CONSULTATION LETTER MLX 272

Proposed amendments to
THE MEDICINES (PRODUCTS OTHER THAN VETERINARY DRUGS) (GENERAL SALE LIST) ORDER 1984 (SI 1984/769) and
THE MEDICINES (SALE OR SUPPLY)(MISCELLANEOUS PROVISIONS) REGULATIONS 1980 (SI 1980/1923)

* 1. We have no comment to make on the proposals in MLX 272.

* 2. Our comments on the proposals in MLX 272 are below/attached.
   - * *My reply may be made freely available.*
   - * *My reply is confidential.*
   - * *My reply is partially confidential (indicate clearly in the text any confidential elements)*

Signed : _____

* Delete as appropriate

Rx Health Value
The Independent Information Center

10 August 2001

Michael Bilirakis, Chairman
Subcommittee on Health
Committee on Energy and Commerce
United States House of Representative
Washington, DC 20515-6115

Dear Mr. Bilirakis:

Thank you again for the opportunity to testify before your Subcommittee on Health on June 13, 2001 regarding "Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals". I must apologize for the tardiness of this response. A clerical error in our office misdirected your letter until just this morning.

Let me attempt brief responses to the questions from your letter of July 19.

1. Do you agree or disagree that the less an individual visits the doctor, the less it costs an insurer? Is it true that the fewer the prescriptions written by doctors participating in health plans, the less it costs the health plan?

In both circumstances described in the question, it is demonstrably not true. In fact, any health plan hoping to survive must encourage both physician visits and appropriate use of prescription drugs. The single most expensive cost factor for any health insurer or health plan will be the costs of hospitalization. Physicians are the best trained and positioned, in terms of patient respect and adherence, to diagnose and treat conditions and diseases which, if not treated in a timely fashion, can lead to more serious illness and much more extensive and expensive interventions, especially hospitalizations. Similarly, with the appropriate use of effective pharmaceuticals, many conditions and diseases can be treated effectively in the out-patient setting with timely use of prescription therapies.

Thus, in both cases, an insurer or health plan which discouraged physician visits and effective pharmaceutical therapy would clearly be operating in a self-defeating manner.

2. Is it better for an individual with an undiagnosed health problem to see a physician before that problem results in serious illness? And if seeing a prescription drug ad on TV, or reading one in a magazine, prompts such a doctor's visit, isn't that a good thing for the public health?

The fallacy in these linked questions lies in the implied causal connection between the TV or magazine ad for a prescription drug and the doctor's diagnostic intervention. First, TV ads for pharmaceuticals are of such short duration that the complex information necessary for an informed patient choice is simply unavailable. Attempts to connect TV ads for drugs with improved public health is simply not worthy of response.

Magazine ads, where the content is prescribed by regulation, considerably more complete and the reader has multiple opportunities for rereading and review, are a different matter altogether. It is, and has been, the position of RxHealthValue that direct-to-consumer advertising of prescription drugs can and should be beneficial to patients. It is the content of the advertisement, its comprehensibility (as tested empirically), and its accuracy, which concerns our coalition members.

625 Indiana Avenue, NW, Suite 200, Washington, DC 20004 • *phone* 202.393.0557 • *fax* 202.393.0497 • *email* RxHealthValue@aol.com

3. Wouldn't you agree that patients with chronic illnesses benefit from increasing research information and knowledge? For example, we recently learned that the National Heart, Lung, and Blood Institute now is changing the definition of "high cholesterol", so people whose cholesterol levels were once thought to be "normal" should be talking with their doctors about taking medicine. If one of these individuals sees an ad for a cholesterol-lowering medication on television, which keeps that person's arteries from clogging and requiring surgery, wouldn't we be reducing health care costs?

Because all its constituent organizations believe in and support increasing patient and consumer knowledge and empowerment in seeking and implementing effective therapies, RxHealthValue continues to support the improvement in the content information in direct-to-consumer advertising of pharmaceuticals. Obviously, we desire the quickest and more comprehensive implementation of research results for the benefit of patients and their physicians. The particular example cited—the so-called "statins", cholesterol-lowering medications, if utilized more extensively, would certainly reduce the incidence of strokes and heart attacks in our population. RxHealthValue is all the more committed to improving the way these medications are presented to the public and to encouraging their appropriate use.

I hope this letter responds to the further questions for the Subcommittee adequately. We hope to be of continuing assistance to you in your work for the American people.

With every best wish, I am

Respectfully yours,

John D. Golenski, Ed.D.
Executive Director

JDG:bd

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August 2, 2001

BY HAND DELIVERY

Honorable Michael Bilirakis
Chairman, Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Bilirakis:

Thank you for the opportunity to respond to the written questions you forwarded following the June 13, 2001 hearing before the Subcommittee on Health on "Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals." My response to each question follows.

1. **Even if Section 503(b)(3) was enacted to harmonize the treatment of prescription and OTC drugs 50 years ago, doesn't a plain reading of the statute indicate the FDA has the authority to force a switch over the objection of a manufacturer?**

The plain language of section 503(b)(3) confirms that this statutory provision does not vest FDA with the authority to force a switch of a single drug over the objection of the drug's manufacturer. Section 503(b)(3) provides FDA with the authority to use rulemaking procedures to switch a particular active ingredient to OTC status in the narrow circumstance where the same active ingredient is marketed and labeled inconsistently by multiple manufacturers for both prescription and nonprescription sale. Section 503(b)(3) permits FDA to "by regulation remove drugs" from the prescription requirements in section 503(b)(1). (emphasis added) The section applies to "drugs" -- plural -- rather than to "a drug." In contrast, section 505(e) addresses procedures relating to a single "drug." This statutory language makes clear that section 505(e) applies (with its hearing and due process protections) when FDA takes action against an individual drug application, and that section 503(b)(3) only applies where FDA is taking action with respect to multiple drugs with a particular active ingredient. This textual reading is directly supported by the legislative history of the provision and 40 years of FDA practice.

2. If the FDA does have the authority to make a switch over the objection of a manufacturer, do you have any thoughts on how this may impact future innovation by the brand industry?

Mandating that a manufacturer sell a drug OTC could significantly affect the drug development process. Drug sponsors establish careful research and development plans for a product's full life cycle. These investment decisions are already quite complex and fraught with uncertainty. Permitting compulsory OTC switches would add further uncertainty to this difficult process. The prospect of an unanticipated switch imposed by FDA or a third party could constitute a material disincentive to drug development in certain areas, and research and investment could be chilled as a result.

3. Realistically, can FDA make the switch without relying upon the cooperation of the drug's manufacturer?

Before any drug can be switched from prescription to non-prescription status, substantial clinical evidence must exist to establish that the drug can be used safely and effectively by consumers without a physician's supervision. Extensive data from prescription use is essential to understanding a drug's clinical profile. As discussed further in number 4 below, it is also critical in most cases that additional data be developed on a drug's use in an OTC setting. The drug's manufacturer is uniquely positioned to know a drug's current clinical profile and to conduct subsequent studies. The manufacturer has the most comprehensive and detailed knowledge of its drug, knowledge that a third party simply cannot possess. For these reasons, it would be highly problematic to proceed with a switch determination without the manufacturer's active cooperation and involvement.

4. If the FDA could switch a drug over the objection of the manufacturer, who would be required to perform label comprehension studies?

It is entirely unclear who -- other than the manufacturer -- would have the expertise with a drug, the resources, and the incentive to conduct new studies to support an OTC switch. Significant issues can arise with OTC use that are not apparent when a drug is administered under a physician's care. Accordingly, FDA typically requires that an OTC switch proposal be supported by "actual use" studies to demonstrate that patients will properly self-diagnose and self-treat in an OTC setting. Label comprehension studies are similarly crucial to show that consumers will understand the risk information presented in the label, including precautions and warnings. It is generally improper to permit a switch without these studies, and no party is as qualified as the drug's manufacturer to do the necessary work.

5. Would it be misbranding if a manufacturer refused to switch its drug to OTC status after being ordered to do so by the FDA?

It is difficult to answer this question without a specific set of circumstances in mind. As a general matter, it is not clear what authority FDA would have to order a manufacturer to switch a single drug OTC. As indicated in number 1 above, there is no such authority under section 503(b)(3). FDA could conceivably assert that a drug is misbranded under section 505(e) when it is labeled for prescription use only and data establish that it can be used safely OTC. However, serious questions could be raised about any argument that a drug is misbranded (false or misleading) because it contains a prescription limitation that potentially provides greater safety for patients. This would also be an unusual use of the statutory provision, which generally addresses the withdrawal of a product due to safety or efficacy concerns. If FDA attempted to use the provision, it would have to provide the manufacturer an opportunity to revise the labeling, provide an opportunity for a hearing, and follow the other procedures outlined in 505(e).

6. What type of process would have to be afforded a drug manufacturer if the FDA wanted to force a switch over the objection of a manufacturer?

Whatever mechanism FDA might attempt to use to force an OTC switch, it would have to provide the manufacturer notice and an opportunity for a formal evidentiary hearing. This is required by section 505(e) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), as well as general principles of administrative law and constitutional due process. In addition, FDA could not use or disclose proprietary data from the manufacturer in a manner that would violate the FDCA, the Freedom of Information Act, the Trade Secrets Act, or the Takings Clause of the United States Constitution.

7. How do the notice and hearing requirements contained in Section 503 of the Food and Drug Act compare and contrast with the Due Process Clause in the Constitution?

Section 503 itself contains no notice or hearing requirements. Presumably a regulation adopted under the authority of that section would have to comply with the notice-and-comment requirements for informal rulemaking under the Administrative Procedure Act ("APA"). However, the minimal APA requirements do not mandate any hearing and certainly are not a substitute for the formal (on the record) hearing that is required under the FDCA, long-established principles of administrative law, and the Due Process Clause of the United States Constitution before the agency could take action against an individual approved license.

8. In your testimony, you state that the FDA would have to rely on manufacturer proprietary data to effectuate a switch, and that "the unauthorized appropriation of proprietary data would implicate the Takings Clause of the Constitution." Under Takings Clause jurisprudence, however, to be a Taking you must render the property virtually value-less. In the case of a forced switch, manufacturers could still derive value by selling their drugs OTC. How then would this be a Constitutional Taking?

Trade secrets and confidential commercial information in an approved drug license are "property" protected by the Fifth Amendment to the United States Constitution. Government action constitutes a per se taking of that property if it deprives the property of all economically beneficial use, or if it constitutes an appropriation of one or more of the property owner's fundamental ownership rights in the property, including the right to exclude others from using the property. In addition, a "regulatory taking" can occur where government action interferes with "reasonable investment-backed expectations," even if the action does not deprive the property of all value. FDA's reliance on and disclosure of a manufacturer's proprietary data (as would be required were FDA to try to effectuate a switch by rulemaking without the manufacturer's consent) implicates these fundamental Takings principles. Disclosure of trade secrets and confidential commercial information compiled by a manufacturer during the testing of an investigational new drug and submitted in a new drug application would allow a competitor to duplicate its research without the same expenditure of time or money, or allow it to avoid that research altogether. This would have a devastating impact on the manufacturer's ability to use that information profitably in a commercial setting, and would upset the reasonable expectations the manufacturer had when it invested in developing the data in the first instance.

* * *

I hope that these responses are helpful. I would be pleased to answer any other questions or to supply any additional materials requested by Members or Subcommittee staff on these or any other issues.

Yours sincerely,

Richard F. Kingham /mse

Richard F. Kingham

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

August 10, 2001

Honorable Michael Bilirakis
Chairman, Subcommittee on Health
Committee on Energy and Commerce
Washington, DC 20515-6115

Dear Chairman Bilirakis,

Enclosed are responses to the to the follow-up questions posed by members of your committee following the June 13, 2001 hearing on "Recent Developments Which May Impact Consumer Access to, and Demand for Pharmaceuticals."

Thank you for giving Mr. Downey the opportunity to testify and submit these answers.

With best wishes,

Sincerely,

Jake Hansen
Vice President for
Government Affairs

Questions & Responses
Regarding Mr. Bruce Downey
Barr Laboratories, Inc.

Question 1: ***Alfred Engelberg, who negotiated Hatch-Waxman on behalf of the Generic industry, now says that the 180-day generic exclusivity is no longer necessary. Rather, he claims that market forces result in many generic manufacturers lining up to challenge patented drugs, and the 180-day generic exclusivity "has become a barrier to generic competition rather than the spur to competition which was intended by the '84 Act.'" Since it is a public good to have generic drugs in the marketplace, why not let all of the potential generic competitors into the market as quickly as possible by doing away with generic exclusivity?***

Response 1:

Mr. Engleberg's conclusion is wrong. Without the incentive of 180-days of generic exclusivity, there would be no "manufacturers lining up" to make the investment necessary to bring products to market years ahead of patent expiry. The incentive of Hatch-Waxman drives the investment in new product development, in patent review, and balances the risk of bringing these complex patent cases. Because of this incentive, consumers have greatly benefited from these pro-consumer and pro-competitive patent challenges. Removing the incentive would make it economically unattractive for any company to make the multi-million dollar, multi-year investment necessary to support a patent challenge case, with its attendant risk of financial failure.

For example, Barr's successful patent challenge cut the expected patent life of Prozac® by about 3 years, saving consumers more than $4 billion dollars. Yet, without the potential for the 180-day reward, Barr would not have invested in this challenge and consumers would have lost the opportunity for substantial savings.

Every successful generic patent challenge creates by its very nature a consumer benefit. The introduction of even a single competitor results in savings for consumers years earlier than would otherwise have occurred.

Simply put, without the 180-day exclusivity reward, generic firms would have no sound business reason to bring a patent case. Generic exclusivity rewards this investment, and, when successful, results in millions of dollars in savings for consumers years earlier than would otherwise be possible.

It is also important to note that in the intervening 17 years since the enactment of Hatch-Waxman, innovator firms have become more successful at manipulating the system's loopholes; such as abusing the 30-month stay provision by listing successive patents in the Orange Book. Hence, the need for the 180-day incentive is even greater today than when Hatch-Waxman was enacted.

Question 2: ***In a September, 2000 article in "Forbes," Barr Labs was referred to as "lawyers in lab coats." "Forbes" estimates that 60% of Barr's revenues are derived from products released for sale after settlement of litigation. In fact, Barr highlights the importance of patent litigation, and litigation settlements, to its business on its website. Would you agree that litigation is important to your company's financial success?***

Response 2:

Each of Barr's successful patent challenges has been pro-consumer and pro-competitive. If we had not pursued the Prozac challenge, we would not have been able to launch generic Prozac® three years ahead of patent expiry at a multi-billion dollar savings to consumers. If we had not pursued our challenge of the patents protecting Tamoxifen, consumers would not have had a lower cost alternative to the brand product ten years ahead of time and would not have saved millions. Our ciprofloxacin patent challenge will result in the introduction of a more affordable generic six months prior to patent expiry. It is clear from these examples that the patent challenge component of Barr's business strategy creates a significant consumer benefit.

Patent challenges, however, are only one component of our business strategy of bringing lower cost generic therapies or proprietary products that offer significant new advantages to American consumers. Our strategy includes the development of distinctive generic pharmaceuticals, which create significant savings to consumers in such therapeutic categories as the treatment of heart disease and cancer. It includes the development of generic products that become the basis of patent challenges, which have the potential of bringing dramatic savings to consumers. And finally, it includes the commercialization of new and distinctive proprietary products that are currently not available to American consumers.

Question 3: ***The FTC is exercising its broad authority to review settlements between generic and innovator drug companies. Why isn't this oversight sufficient? Why do you believe that Hatch-Waxman needs to be amended to address this issue?***

Response 3:

Hatch-Waxman does not need to be amended to address the issues being considered by the FTC.

We believe that Hatch-Waxman reform is necessary to address other issues, namely the ability of brand pharmaceutical companies to evergreen patents and significantly delay the introduction of more affordable generic medicines by "gaming" the legal and regulatory processes.

We applaud the recent efforts of Congress to consider ways to restore the original 1984 Hatch-Waxman balance that has been disrupted by the ability of brand companies to use a multitude of tactics to preserve market exclusivity.

Question 4: ***The Brown-Emerson legislation would require the Federal Trade Commission to open an investigation any time a person complains that a Citizen Petition filed with the***

FDA was filed for an improper purpose. Isn't this an incredibly low standard to compel an FTC investigation?

Response 4:

While it is our understanding that this provision is designed to address the submission of frivolous Citizen Petitions, Barr favors other reform means over this approach. We support the notion that ANDA review and approval should not be delayed unless a Citizen Petition demonstrates that ANDA approval would present an imminent hazard to the public health.

Question 5: How common is it for a generic which is the first to file a paragraph IV certification to delay marketing in exchange for payments from the innovator?

Response 5:

In Barr's experience, such arrangements are not common in the industry. In addition, your question appears to assume that the paragraph IV filer would have gone to market in the absence of payments from the innovator. This is not necessarily true.

In many patent challenge cases it is undisputed that the generic product infringes the patent (for example, when the innovator holds a "compound" patent, that is, one that covers the chemical composition of a drug). Under such circumstances, the only time that a generic would bring a product to market would be if the patent were held invalid or unenforceable by a court. Otherwise, a generic competitor would be violating the law and subject to crippling damages.

In order for a patent to be invalidated, the generic competitor must be successful in pursuing litigation to a final decision, where a court of competent jurisdiction rules that the patents are invalid or unenforceable. If the generic fails to invalidate the patent, it cannot market the product. Of course, as in all litigation, both the generic and the innovator face some risk of losing the litigation. Throughout the legal process, the American judicial system encourages the settlement of lawsuits where possible, and neither party is obligated to litigate to a final conclusion. Such settlements may, in the patent-challenge context, involve settlement payments in consideration for litigation risk as well as expense posed by the patent challenge. The fact that litigants agree to a settlement has no impact on the existing patent protection, so that the only marketing the generic will be entitled to, if any, is that obtained in the negotiated settlement.

Our corporate history demonstrates that Barr has undertaken six patent challenges: Barr won two, lost two, and settled two cases. Both of the settled cases involved compound patents, in which there was no dispute that Barr's product infringed the innovators' patents. Both settlements terminated the respective lawsuits (thus conserving judicial resources) and were limited to the products in question. Under both of the settlements, Barr obtained the right to launch competitive products into the marketplace under license arrangements with the innovators at some point prior to patent expiration. For example, in the Tamoxifen® case, Barr provided consumer access to a competitive generic product ten (10) years prior to the expiration of the

brand patent. Our ciprofloxacin patent challenge will also result in the introduction of a more affordable generic six months prior to patent expiry. Moreover, in both of those cases, subsequent generic companies challenging the same patents lost.

Accordingly, settlements undertaken by Barr have yielded significant economic and therapeutic benefits to consumers. These settlements clearly provided greater benefits than would have been achieved if Barr had continued those cases and lost. Moreover, freeing up the considerable resources that were involved in such cases enabled Barr to concentrate on other product development and patent challenge efforts, such as the one on Prozac®, which cut the expected patent life by about three (3) years, saving consumers more than $4 billion.

Question 6: How concerned are you that the average American consumer may not recognize that a generic drug is bioequivalent to an innovator drug? What can be done to increase consumer awareness?

Response 6:

Recent surveys confirm that 83% of Americans have no bias against generic drugs; yet, only 54% fill their prescriptions with generics. A recent study by the Managed Care Institute of Samford University suggests that a very modest 1% increase in the usage of generic drugs would result in additional healthcare savings of more than $1 billion. Given the remarkable economic and health benefits of generic drugs for consumers, a multi-faceted, national education effort is required.

The generic industry, through organizations such as the Generic Pharmaceutical Association and its predecessors, have made great strides in the past 5 years towards educating the public concerning generic drugs. Yet, we simply cannot do it alone. Sufficient funding should be provided to FDA to conduct an orchestrated education program on the safety and efficacy of generic drugs, and to take enforcement actions against brand companies who make misleading statements about generic products. It is critical that Americans have the utmost confidence in the safety and efficacy of the drugs approved by FDA, whether the drugs are brand or generic.

We believe that there should be consequences for any company that suggests that generic pharmaceutical products do not provide the same safety and efficacy as their brand equivalents. Over the past several years, brand companies have been attacking the FDA's bioequivalence policy on numerous fronts. Their goal has been to undermine the public's confidence in the FDA and its bioequivalence determinations. Regrettably, many of these anti-generic campaigns have had indirect consumer effect. Additional funding is needed and FDA should be encouraged to proactively defend its bioequivalence policies and its therapeutic equivalence determinations at both the Federal and State levels (e.g., State Boards of Pharmacy).

In today's healthcare climate, access to, and use of, affordable generic drugs could provide significant cost relief. It is imperative, therefore, that the public be educated on the remarkable public health and economic benefits of generic drugs, and of the FDA's rigorous drug approval processes.

Question 7: ***Do you agree that the cost of researching and developing a new drug is approximately $500 million and that cost is increasing each year? What is the approximate cost incurred by a generic drug company on the bioequivalent testing and formulation development needed to bring a generic drug to the market?***

Response 7:

Based on our experience, the cost for the development of a generic drug can range anywhere from $250,000 to $10 million, and take anywhere from 1-5 years to develop and receive approval.

Despite repeated claims by PhRMA, we believe that the $500 million estimate is vastly inflated. A recent Public Citizen report concluded that, based the brand industry's own figures, the actual cost is closer to $100 million per new drug product. See Public Citizen, Rx R&D Myths: The Case Against The Drug Industry's R&D "Scare Card" (July 23, 2001).

Unfortunately, the issue of the cost of developing new drugs is often used by the brand industry to support its argument that additional market exclusivity is appropriate, and that generic competition is harmful to the development of new drugs.

We believe, and our conclusion has been supported by the 1999 Congressional Budget Office Study of generic competition, that competition promotes innovation. The CBO Study concluded, "1983 and 1995, investment in R&D as a percentage of pharmaceutical sales by brand name drug companies increased 14.7 percent to 19.4 percent. Over the same period, U.S. pharmaceutical sales by those companies rose from $17 billion to $57 billion."

In the debate on health care costs, the issue of R&D spending should be set aside. Brand pharmaceutical companies are among the most profitable businesses in the world, and competition promotes innovation and helps consumers save money. Congress' attention might be better spent on ensuring fair and timely generic competition, increasing generic substitution rates, and closing the loopholes that enable brand companies to patent invalid claims or unfairly extend monopoly protection.

Question 8: ***The FTC is exercising its broad authority to review settlements between generic and innovator drug companies, and should complete their investigative report by the end of this year. Do you believe that Hatch-Waxman should be amended before Congress has the opportunity to benefit from reviewing this report?***

Response 8:

Hatch-Waxman reform is urgently needed to accelerate the introduction of more affordable pharmaceuticals. The current system has too many loopholes that are being exploited to block the availability of generic drugs.

The fundamental issue at the heart of the Hatch-Waxman reform is the need for Congressional action to restore the optimal balance between encouraging innovation and accelerating the availability of generic drugs. Given the historic, as well as recent, manipulations of the current ANDA approval system, it is in the public's best interest to immediately restore the system's balance by pursuing reform initiatives.

Question 9: ***Isn't it true that patents are issued only if the Patent and Trademark Office determines that they meet all legal requirements? Isn't it also true that innovator drug manufacturers are subject to penalties if they make a false settlement to obtain a listing in the Orange Book?***

Response 9:

Barr fully supports intellectual property rights and the Constitutional rights afforded patent holders. We do not agree with the assessment that patents are issued only if they meet all legal requirements.

Like any large organization, the Patent and Trademarks Office is not infallible. For example, there have been instances of "double-patenting" where a patent was issued for an already patented invention. See Eli Lilly v. Barr Laboratories. In other cases, the inventor of the patent is not the actual first inventor. Other times, a patent appears to be properly issued but is later determined to be invalid in light of facts unknown to either the applicant or the PTO at the time of filing (e.g., the existence of prior art). Finally, sometimes it is the applicant, rather than the PTO, who is at fault for the issuance of an invalid patent.

The problem with the issuance of patents regarding pharmaceutical products is two-fold. First, the non-adversarial nature of the patent process precludes raising issues of validity until after the patent is issued. Second, there are no current restrictions on the number and timing of the listing of patents, which in effect, allows the brand pharmaceutical company to indefinitely extend its market exclusivity through add-on patents.

While there are, at least in theory, penalties for the submission of patents that clearly do not claim the approved drug or its approved uses, those penalties have never been enforced. Likewise, the FDA has stated that it believes the only current remedy for an improper patent listing under the FDCA is the withdrawal of the submitter's NDA approval – a penalty the agency has decided is too draconian and contrary to the public health, and therefore is unlikely ever to be imposed. Thus, there is no effective regulatory deterrent to the submission of improper patents for listing in the Orange Book.

Question 10: ***Has any generic drug company ever filed a Citizen Petition with the FDA? Over the last five years, how many have been filed by generic companies, or persons acting on behalf of a generic drug manufacturer? Has the Generic Pharmaceutical Association or any of its predecessor organizations ever utilized the citizen petition process? If so, how many times over the last five years?***

Response 10:

In a review of petitions filed during the past 18 months, the vast majority of Citizens Petitions filed by generic industry associations or members have been requests to FDA to file ANDAs for different strengths and dosage forms other than that of the brand product. The industry has also filed a number of petitions requesting clarification by the Agency of the withdrawal of brand products. Two petitions have concerned general policy issues.

The problem with the Citizens Petition process is when it is used to block the introduction of lower cost generic products. These anti-competitive actions by brand companies can often result in the addition of months of market exclusivity, at great expense to consumers, but when no safety risk or health concern exists.

Question 11: ***The FDA has the unilateral authority to dismiss any frivolous Citizen Petition. Isn't this sufficient to deal with the alleged problems associated with Citizens Petitions being filed by innovator drug companies?***

Response 11:

Regarding citizens petitions, we fully respect the Constitutional right of all citizens to petition the government to address genuine issues of concern. The concern we have is the misuse of the petition process to forestall generic drug approvals in an effort to delay competition.

Any citizen petition that meets FDA requirements (21 C.F.R. § 10.30(b) (2001)) must be accepted for filing regardless of when the petition is filed with the agency. The industry's primary concern involves citizen petitions filed shortly before, or on the eve of, generic approval that have the potential for delaying or blocking timely approval and consumer access to generic pharmaceuticals.

Barr endorses the concept that citizens petitions should not be permitted to delay the approval of generic applications, unless a petition contains substantial scientific evidence establishing that approval of the generic product would cause an imminent hazard to the public health.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 16 2001

The Honorable Michael Bilirakis
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Chairman Bilirakis:

Thank you for your letter of July 19 in follow-up to the hearing before the Subcommittee on Health on June 13, 2001, "Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals" at which Dr. Janet Woodcock testified on behalf of the Food and Drug Administration. We apologize for the delay. As was discussed in a telephone call on August 3 between Diane Prince of my staff and Marc Wheat of your staff, this response was delayed due to technical problems in the letter being transmitted to the Office of Legislation. We did not received until August 3.

The responses to the questions submitted are enclosed as Attachment A.

Thank you for making this a part of the public record.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosure

Questions from Rep. Ralph Hall

1. I understand from testimony at the subcommittee hearing that insurance companies currently reimburse for prescription, second-generation antihistamines but that the insurance companies are unlikely to reimburse if the products are OTC. Has FDA considered whether patient access to second-generation antihistamines will decrease if patients have to pay for these products out-of-pocket? Will use of first-generation antihistamines (which will presumably be less expensive than the second-generation) increase? While I understand that cost is not a consideration in a switch decision, it seems to me that increased utilization of first generation antihistamines does present safety and public health issues that should be considered. I would appreciate your views on this issue.

As you correctly state, FDA does not consider costs in approval or Over-the-Counter (OTC) switch actions. The Federal Food Drug & Cosmetic Act (FD&C Act) gives us the authority to evaluate the safety and effectiveness of a drug. We do not evaluate the cost issues. In considering a potential Food and Drug Administration (FDA or the Agency) initiated switch in the marketing status of the second-generation antihistamine drugs in response to the Blue Cross (Wellpoint) Citizen Petition, consideration would have to be given to public health impact of such an action. Increased utilization would be an issue for FDA to consider for possible safety and public health impact. We understand the concerns you have expressed about possible relative costs of the second-generation versus the current OTC antihistamine and the resultant potential shifts in market share, however, we cannot comment on the likelihood of whether such scenarios would or would not occur, nor the public health impact that might result.

2. From the testimony given at the subcommittee hearing, it seems that there are many policy and legal issues involved with a forced switch. Resolution of these issues could take time and Agency resources. Why doesn't FDA simply sit down with the companies involved, and discuss the data and studies they believe to be necessary to take these products OTC?

FDA does routinely meet with sponsors of drugs to discuss matters such as a switch to OTC status. If FDA were to move towards granting the Citizen Petition and therefore switching the status of the drugs in question to OTC status, it would be

advantageous to meet with the sponsoring companies to facilitate this change. Your question, however, relates to discussing with the companies involved any data or studies necessary to take these products OTC. At the May 11, 2001, joint Non-Prescription Drugs and Pulmonary-Allergy Drugs Advisory Committee meeting, which considered the OTC switches, FDA made clear, and the committee concurred in their voting, that no actual-use studies or additional data would be needed for an OTC switch, given the accepted role of antihistamines for the treatment of allergic rhinitis in the OTC setting and the safety record of these three drugs. While labeling comprehension studies may provide useful information for any OTC switch, there is acceptable monograph labeling for OTC antihistamines that could be used as a basis for labeling of these products, were they to be switched. Therefore, we would not view any further studies as "necessary" to the switch.

Questions for Dr. Janet Woodcock

1. If the 180-day generic exclusivity provision is never triggered by the holder of the exclusivity through marketing or a court decision, then in effect the first challenger of a patent can keep other generics off of the market if it is sued by, and then settles its litigation with, the innovator, isn't that correct?

There are circumstances in which this could occur. If there is no court decision and the first applicant holding the 180 day exclusivity does not begin commercial marketing of the generic drug product, there may be prolonged or indefinite delays in the beginning of the marketing exclusivity period and delays in the marketing of subsequent generic products. The situation depends on whether actions taken by the generic company constitute marketing or a court decision.

2. Prior to the Mova decision, to be eligible for the 180 days of generic exclusivity a generic manufacturer had to both be the first to file a Paragraph IV certification, and then successfully defend suit in court. Now all a generic manufacturer has to do is to be the first to file and be sued to be solely eligible for the exclusivity. Has the Mova decision led to an increase in litigation? If so, should Mova be overturned by the Congress?

Since the decision in Mova, a generic company does not need to be the first to file and be sued in order to be solely eligible for the exclusivity, the company merely needs to be the first to file. Since Mova, there has been an increase in litigation involving the Paragraph IV certification and patent listings. Whether all of the lawsuits are a direct result of Mova is not a conclusion FDA can make. In light of the court decisions finding certain FDA regulations inconsistent with the statute, the Agency proposed new regulations in August 1999, to implement the 180-day exclusivity. Since then many comments have been submitted and there have been additional court decisions further interpreting the 180-day exclusivity provision and complicating the regulatory landscape. Thus, Mova is not the only case at issue at the current time. The Agency has not yet published a final rule on 180-day exclusivity. As described in a June 1998, guidance for industry, until new regulations are in place, FDA is addressing on a case-by-case basis those 180-day exclusivity issues not addressed by the existing regulations.

3. Does the FDA believe that the "rolling" exclusivity provision contained within the Brown-Emerson legislation would be an impediment to generic competition in that the exclusivity would continue to bounce from the first to the second to the third challenger?

The Administration has not taken a formal position on the Brown-Emerson legislation. In the preamble to FDA's proposed rule on 180-day exclusivity, published August 6, 1999, 64 FR 42873, 42875, FDA indicated it had considered adopting an interpretation of "rolling exclusivity" but had retained the original interpretation allowing only the first applicant to have the marketing exclusivity. A rolling exclusivity, as interpreted by FDA, would roll from applicant to applicant if not utilized and thus could delay the introduction of any generic product into the market.

Questions from Representative Peter Deutsch

1. In the action brought in Florida by Andrx Pharmaceuticals, Inc. against a Canadian pharmaceutical company called Biovail, the FDA stated that, when Biovail first listed its patent in January 2001, the agency was led to believe that Biovail was listing the patent based on the approved drug product Tiazac. When Biovail then revealed on February 26, that it had listed the patent based on an unapproved formula of Tiazac, the agency said that it "was prepared unilaterally to delist the patent" because "FDA is now of the view that the ˜463 patent does not claim the approved drug product as required by the statute and therefore cannot be listed in the Orange Book for Tiazac." Counsel for FDA also told the Federal judge that FDA was prepared unilaterally to delist the patent. Why didn't FDA follow through and delist the patent immediately once it learned that Biovail had misled the agency about the basis for the listing?

Andrx filed its lawsuit over the listing in the Orange Book of the '463 patent after Biovail refused to withdraw the patent following a challenge by Andrx pursuant to Title, 21 Code of Federal Regulations §314.53(f). Andrx sought, in a Motion for Preliminary Injunction, among other things, that Biovail request that FDA remove the '463 patent from the Orange Book to permit approval of Andrx's ANDA for diltiazem hydrochloride extended-release capsules (generic Tiazac). On March 6, 2001, the District Court issued an Omnibus Order denying Andrx's motion. The Court's ruling was based on its conclusion that it did not have subject matter jurisdiction at that time over the claims advanced by Andrx, and, thus, had no authority to grant the requested relief. The Court determined that the FD&C Act did not allow the Court to intervene, at that time, in the dispute over the listing of the '463 patent.

In support of its Motion to Dismiss and in response to Andrx's Motion for Preliminary Injunction, FDA took the position in a pleading, filed on February 26, 2001, that the Agency was not a proper party to the suit because FDA only has a ministerial role with regard to listing patents under the statute and FDA regulations. That same day, Biovail also filed a pleading with the District Court, that raised serious questions for FDA regarding Biovail's understanding of the characteristics and identity of the approved Tiazac product. The identification of the approved drug, unlike the resolution of patent issues, is squarely within FDA's jurisdiction. FDA alerted the Court in a filing on February 28, 2001, that as a result of a

preliminary review of Biovail's pleading, there was a question as to whether the patent filing made by Biovail did specifically apply to the approved drug product, as required by law. In its filing, FDA notified the court that **if** the representations made by Biovail were correct, then it appeared that the '463 patent did not apply to the product approved in the NDA. At the March 1, 2001, hearing on Andrx's Motion for Preliminary Injunction, FDA informed the Court that if the patent did not apply to the approved drug product, then FDA would **consider** delisting the patent. (A copy of the relevant portion of the transcript is enclosed at Tab A.)

The District Court Omnibus Order issued shortly thereafter stated that it was an interim, jurisdictional decision, and the Court gave FDA until March 30, to respond to a pending Andrx Motion for Partial Summary Judgment and to make any changes in the Motion to Dismiss filed by FDA.

FDA moved quickly to address and resolve the issues raised in the preliminary hearing in order to provide information on FDA's position to the Court by March 30. Immediately after the Court's decision, Biovail requested that the company have an opportunity to meet with FDA to provide data and information to support the company's contention that the changes described in their pleadings were not major manufacturing changes that would require pre-approval by FDA. FDA reviewed the Tiazac NDA and the additional information provided by Biovail and met with the company on March 20.

As a result of FDA's review of all relevant information, the company was notified by FDA on March 23, that the manufacturing changes described by Biovail had not been approved by FDA and constituted a major manufacturing change. Thus, FDA explained that the described manufacturing changes resulted in a new unapproved drug product that would require Biovail to submit a supplemental application for FDA's approval before that drug product could be marketed.

FDA also informed Biovail that, in light of the Agency's clarification of the identity of the approved drug product, Biovail must state whether the '463 patent covered the approved drug and provide a signed declaration, as required by law, stating that the '463 patent claims the approved Tiazac product. The company was reminded that submitting a false declaration of material fact was subject to prosecution under Title 18, U.S.C. §1001. Biovail also was informed that if the signed declaration was not received by 5:00 p.m. on Monday,

March 26, FDA would consider the '463 patent to have been withdrawn by the company.

In response to FDA's letter of March 23, Biovail submitted a signed declaration, within the time requested, stating that the '463 patent was eligible for listing in the Orange Book as relating to the new drug application (NDA) approved product, Tiazac. Once Biovail reconfirmed the accuracy and relevance of its patent listing, FDA's ministerial function was completed. Thus, the '463 patent remains listed in the Orange Book.

FDA filed additional information with the District Court in the *Andrx case* on March 30. The Agency submissions described in further detail its actions with respect to the Tiazac NDA and the listing of the '463 patent. A copy of these March 30 pleadings is enclosed. (Tab B)

2. FDA regulations specify that, in order to lawfully list a patent in the Orange Book, the applicant "shall submit the following declaration:

> **The undersigned declares that Patent No._____ covers the formulation . . . of [the approved drug product]. This product is currently approved under section 505 of the Federal, Food, Drug, and Cosmetic Act." 21 C.F.R. §314.53(c)(2)."**

FDA has admitted in the Federal court proceeding that Biovail did not submit such a declaration on January 8, 2001. FDA also specifically told Biovail that Biovail could not lawfully list the new Tiazac patent unless such a declaration was submitted. Is it now FDA's position that Biovail's incomplete and unlawful listing in January was valid? How could the FDA allow this?

Biovail did provide a declaration when the patent was filed with FDA. In cases in which the identical language of the regulation is not utilized, FDA customarily asks for clarification to ensure that the patent does cover the formulation of the approved product. Biovail submitted a signed declaration, within the time requested by FDA, stating that the '463 patent was eligible for listing in the Orange Book as relating to the NDA approved product, Tiazac.

3. The Federal judge found that Biovail had expressly stated that it was listing a new patent in FDA's Orange Book "because Biovail has recently changed its manufacturing of Tiazac" to include the active ingredient in an "uncoated form."

Counsel for FDA himself stated at a hearing in the Florida case that Biovail's statements "seem to fairly clearly indicate to the agency that the drug that this patent claims is not the drug that was approved in the New Drug Application, but a different formulation, which would make it a different drug product."

On what legal basis did FDA then allow the same Canadian company to list the same patent only twenty days later as "claiming" the unchanged, approved formulation of Tiazac?

As noted in the response to Question 1, Biovail submitted a signed declaration, within the time requested by FDA, stating that the '463 patent was eligible for listing in the Orange Book as relating to the NDA approved product, Tiazac. The conclusion by FDA that the manufacturing changes described by Biovail had not been approved by FDA and constituted a major manufacturing change did not mean that the patent did not cover the approved drug product, Tiazac. Once Biovail reconfirmed the accuracy and relevance of its patent listing, FDA's ministerial function was completed. Thus, the '463 patent remains listed in the Orange Book.

4. Under Federal law, a patent cannot be listed in the FDA Orange Book unless it "claims" a drug product approved by FDA. Yet Biovail's lawyers specifically stated to the Florida Federal court that Biovail's approved drug product, Tiazac, is "not within the literal meaning of the patent." Why did FDA keep the unlawfully listed patent in the Orange Book instead of immediately taking it out after Biovail made it clear that the patent did not claim the approved drug Tiazac as required by law?

As noted in the response to Question 1, Biovail submitted a signed declaration, within the time requested by FDA, stating that the '463 patent was eligible for listing in the Orange Book as relating to the NDA approved product, Tiazac. Once Biovail reconfirmed the accuracy and relevance of its patent listing, FDA's ministerial function was completed. Thus, the '463 patent remains listed in the Orange Book.

5. In following the maze of FDA's logic in this matter, one can only conclude that the FDA has placed its bureaucratic concern that it not get involved in patent matters ahead of its obligation to fairly and equitable administer the laws that this Congress enacts. It seems that the FDA's actions in this matter fall completely outside the scope of what Congress intended.

If the FDA allows a company to list a patent in the Orange Book that FDA itself knows to be ineligible because it does not meet the minimum requirements of the law -- that is, that the new patent apply to the drug in question - thereby forestalling generic competition for up to two and one half years, does not the FDA, in effect, invite every unscrupulous company to follow suit? And does that not make the FDA an active partner in the process of undermining the law Congress created to help its citizens get generic medicines in a timely manner?

Please do not respond to this question citing the importance of intellectual property. Members of Congress already share the FDA's commitment to protect the product of human ingenuity. Section 4 of the Waxman-Hatch Act is designed to protect legitimate innovations even when they come long after the drug has been on the market. That is not the issue here. The issue here is a patent that is listed falsely by the FDA in the Orange Book. The patent is listed falsely because in this case the FDA itself declared to a Federal District Court that the patent did not apply to the drug and therefore should not be listed. Yet, at a later date, the FDA decided it was the easier course for it to list the patent than take the action required by the law which is not to list a patent that does not qualify. Please explain these decisions.

It is a long-standing position of FDA that its responsibility with respect to patent listings in the Orange Book is of a ministerial nature. The patent certification process means there is the possibility of a considerable delay in the approval of ANDAs as a result of new patent listings. FDA regulations provide that, in the event of a dispute as to the accuracy or relevance of patent information submitted to and subsequently listed by FDA, an ANDA applicant must provide written notification of the grounds for dispute to the Agency. FDA then requests the NDA holder to confirm the correctness of the patent information and listing. Unless the patent information is withdrawn or amended by the NDA holder, FDA will not change the patent information listed in the Orange

Book. An ANDA submitted for a drug, for which the patent is listed in the Orange Book, must therefore contain an appropriate certification regarding the patent, despite any disagreement as to the correctness of the patent information.

The statute requires FDA to publish patent information upon receipt. FDA is not required to take any other action with respect to the patent or otherwise look beyond the face of the submitted patent information. Instead, generic and innovator firms are left to resolve any patent disputes concerning a drug in private litigation. FDA has implemented the statutory patent listing provisions by informing interested parties what patent information is to be submitted, who must submit the information, and when and where to submit the information. FDA's regulations on these issues are found at 21 CFR §314.53.

FDA's ministerial approach in listing patents has been upheld in U.S. District Court. In *Watson Pharmaceuticals, Inc. v. Henney and Bristol- Myers Squibb Co.*, Civ. No. S-00-3516 (D. Md.), the Court explained in a March 13, 2001, memorandum opinion:

> [I]t is paramount to keep in mind that FDA, in deciding to make an Orange Book listing, is *not* acting as a patent tribunal. It has no expertise - much less any statutory franchise - to determine matters of substantive patent law. In making its decision to list a patent, therefore, it is entirely appropriate and reasonable for FDA to rely on the patentee's declaration as to coverage, and to let the patent infringement issues play out in other, proper arenas, as is the clear intent of the Hatch-Waxman Amendments. In fact, the legislation clearly reflects that Congress recognized that FDA has a very limited, ministerial role in patent fights between patentees and generic marketers - that of taking information from the patentee, publishing that information in the Orange Book, and awaiting the institution and/or outcome of patent litigation.

(Opinion is enclosed at Tab C.)

FDA does not assess whether a submitted patent claims an approved drug and whether a claim of patent infringement could reasonably be made against an unauthorized use of the patent drug. As the Agency has stated, since the implementation of the 1984 Hatch-Waxman Amendments began, FDA has no expertise

or resources with which to resolve complex questions of patent coverage, and thus the Agency's role in the patent-listing process is ministerial. *See*, 54 FR 28872, 28908-11 (July 10, 1989); 59 FR 50338, 50342-45 (October 3, 1994). The Agency relies on the NDA holder or patent owner's signed declaration stating that the patent covers an approved drug product's formulation, composition or use. FDA does not scrutinize the basis of the declarations provided by NDA holders concerning their patents, so long as all of the required information has been submitted.

(Call to order of the Court.)

THE COURT: Andrx versus Biovail. If counsel would slowly announce their appearances for the record.

MR. ISICOFF: Your Honor, for Andrx, Eric Isicoff of Isicoff, Ragatz & Koenigsberg, Miami, Florida. Present with me are me Louis Solomon, Colin Underwood and Jennifer Scullion of the Solomon, Zauderer firm in New York.

And Mr. Solomon will be presenting the argument for the plaintiff.

THE COURT: Okay.

MR. RAUCHBERG: Good morning, Your Honor. Ronald Rauchberg, Proskauer Rose, for defendant Biovail. And with me at counsel table also from Proskauer are, to my right, Michael Cardozo, and to his right, Matthew Triggs.

Also present in the courtroom is Mr. Kenneth Cancellara, who is the general counsel of Biovail, and other representatives of Biovail.

THE COURT: Okay.

And the Government.

MR. CLARK: Good morning, Your Honor. Andrew Clark from the Justice Department on behalf of the federal defendants. And with me at counsel table is Kevin Fain from the General Counsel's Office of the Food And Drug Administration.

THE COURT: Why don't we address the Federal

1 position. I got a notice of change of position. I guess this
2 morning I got it. And let me ask Mr. Clark. How does that
3 effect your motion to dismiss?
4 MR. CLARK: Your Honor, the federal defendants -- I
5 guess the best way to put it, we still stand by our view that
6 the Complaint does not state a claim against us, and we still
7 stand by our view that even if the Complaint did state a claim
8 against us, that no relief against the federal defendants would
9 be called for here because the agency's actions, based on the
10 information they had at the time, were reasonable and proper.
11 And we still have not taken a position with respect
12 to the merits of Andrx's specific claims against Biovail.
13 But we do and did feel compelled to notify the Court
14 that we have now taken a position regarding the propriety of
15 the listing of the 463 patent that is different from the
16 position we had taken before in that the FDA's practice -- as
17 we indicated in our original papers -- is that we accept the --
18 the agency accepts at face value the statements of the patent
19 holder regarding the claim of the -- what the patent claims and
20 that's why FDA listed the patent in the first place.
21 But since that time, in the pleadings that were filed
22 by Biovail on Monday, they seem to fairly clearly indicate to
23 the agency that the drug that this patent claims is not the
24 drug that was approved in the New Drug Application, but a
25 different formulation, which would make it a different drug

1 product --

2 THE COURT: Let me ask you something. Let's assume

3 Andrx hadn't filed this lawsuit, what would the FDA be doing

4 with this new information, if anything?

5 MR. CLARK: The FDA is not entirely certain what they

6 would do.

7 Certainly they would be seriously considering

8 delisting the patent.

9 They might first seek more information from Biovail.

0 It's pretty sketchy what they have indicated about what their

1 new manufacturing process is, what the new formulation is.

2 But I think the agency would be justified if they had

3 decided to simply delist because they can take the new

4 statements, the representations in the brief, the statements in

5 the declaration, at face value, and if you do that, it would

6 indicate that it's not the drug that they approved in the NDA.

7 So the FDA was actually prepared to unilaterally

8 delist that patent, but given the fact that the litigation was

9 pending, the hearing was pending, and the likelihood that if

0 they did that, then they would be sued by Biovail, and we would

1 just have to change tables, the agency felt that it would be

2 more prudent to await this hearing and see what develops,

3 rather than taking any unilateral action on its own.

4 THE COURT: So do you still want me to rule on the

5 motion to dismiss?

6

1 MR. CLARK: I think that the Court does not need FDA
2 to be a party to the case to resolve the issues that Andrx has
3 raised against Biovail and I think that the Complaint doesn't
4 state a claim against FDA. I don't know that it's necessary
5 for the Court to immediately rule on that motion. And I
6 certainly wouldn't object to the extent the Court feels that it
7 could benefit from FDA's presence or views to deferring that
8 motion to dismiss until, you know, some later date in the
9 Court's discretion.
10 THE COURT: Why should I do the dirty work? If FDA
11 is administratively prepared to resolve this issue -- are you
12 saying that I should do it because it's just going to come back
13 to me or some other Judge if you guys make the decision?
14 MR. CLARK: That certainly was part of the thinking.
15 I mean I think -- that if the agency delists the patent -- I
16 think there is a likelihood that then there will be litigation
17 brought by Biovail against FDA, and that Andrx will intervene
18 if they are not named, and we will be right back before either
19 this Court or another Court, and that in the interest of
20 judicial economy and efficiency, since all the parties are
21 here, we thought it made more sense to not -- to defer taking
22 any action like that, and let the parties be heard on this, and
23 let the Court -- not sort of preempt the Court's role.
24 But certainly the agency -- if this case -- if there
25 were no case, the agency would be prepared to act. Whether

1 that action would be immediately delisting the patent or more
2 likely seeking a little bit more information, I am not
3 certain. Probably the latter.
4 THE COURT: Let me ask Andrx for whatever position
5 they have on this.
6 MR. SOLOMON: Judge, on the motion to dismiss by the
7 Government or more generally on our motion for a preliminary
8 injunction?
9 THE COURT: The motion to dismiss by the Government.
10 MR. SOLOMON: The motion is actually not returnable.
11 And our view on that is that we would oppose the motion to
12 dismiss, but the Government is not a respondent on our motion
13 for a preliminary injunction. We sought no relief against the
14 Government on the motion for a preliminary injunction.
15 The reason that we joined the Government -- we tried
16 to make clear in our papers -- is because in a prior case
17 involving listing, rather than delisting, the Government was
18 not a party, and the Court in that case made a recommendation
19 to the FDA. He said I couldn't order the FDA to actually do
20 something with this patent because the FDA was not a party.
21 That case was in California. When the case got back to
22 Washington, the FDA said thank you. We understand the
23 recommendation, but we are not going to follow it. And we
24 didn't want that to be the case here. We are not looking for
25 other relief against the Government. Indeed, we had suggested

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

ANDRX PHARMACEUTICALS, INC., Plaintiff, v. BIOVAIL CORPORATION INTERNATIONAL, Defendant, and TOMMY G. THOMPSON, Secretary, U.S. Department of Health and Human Services, BERNARD A. SCHWETZ, D.V.M., PhD., Acting Principal Deputy Commissioner, U.S. Food and Drug Administration, and U.S. FOOD AND DRUG ADMINISTRATION, Additional Defendants.	Case No. 01-6194-CV-DIMITROULEAS

FEDERAL DEFENDANTS' MOTION TO DISMISS AMENDED COMPLAINT

Federal defendants Tommy G. Thompson, Bernard A. Schwetz, and the U.S. Food and Drug Administration hereby move pursuant to Fed. R. Civ. P. 12(b)(1) and 12(b)(6) to dismiss the amended complaint against them for lack of subject matter jurisdiction and for failure to state a claim upon which relief can be granted. The grounds for this motion are set forth in the accompanying Memorandum of Federal Defendants in Opposition to Plaintiff's Motion for Partial Summary Judgment and in Support of Motion to Dismiss Amended Complaint, filed herewith.

Dated: March 29, 2001

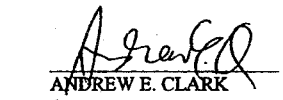
Respectfully submitted,

STUART E. SCHIFFER
Acting Assistant Attorney General

GUY A. LEWIS
United States Attorney

By: BARBARA PETRAS
Assistant United States Attorney

EUGENE THIROLF
Director
Office of Consumer Litigation



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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

ANDRX PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	Case No. 01-6194-CV-DIMITROULEAS
BIOVAIL CORPORATION INTERNATIONAL,	)	
Defendant,	)	
and	)	
TOMMY G. THOMPSON, Secretary, U.S. Department of Health and Human Services, BERNARD A. SCHWETZ, D.V.M., PhD., Acting Principal Deputy Commissioner, U.S. Food and Drug Administration, and U.S. FOOD AND DRUG ADMINISTRATION,	)	
Additional Defendants.	)	

RESPONSE OF FEDERAL DEFENDANTS TO
PLAINTIFF'S STATEMENT OF UNDISPUTED MATERIAL FACTS

Pursuant to Rule 7.5 of the Local Rules of the United States District Court for the Southern District of Florida, the federal defendants respond as follows to Plaintiff's Statement of Undisputed Material Facts:

1. Paragraph 1 is a legal statement to which no response is required.

2. Paragraph 2 is a legal statement to which no response is required.

3. Paragraph 3 is a legal statement to which no response is required, except that the proper citation is 21 C.F.R. § 314.53(b).

4. Federal defendants dispute the statement contained in paragraph 4 in that Tiazac is approved only for the treatment of hypertension and the treatment of chronic stable angina.

5. Federal defendants do not dispute the statement contained in paragraph 5 except to state that the approved Tiazac drug product does not contain any intended amounts of free diltiazem.

6. Federal defendants do not dispute the first sentence of paragraph 6 but lack sufficient knowledge to form a belief concerning the marketing and sale of Tiazac.

7. Federal defendants do not dispute the statement contained in paragraph 7.

8. Federal defendants dispute the statement contained in paragraph 8 in that the 30 month period under 21 U.S.C. § 355(j)(5)(B)(iii) that resulted from the filing of patent 5,529,791 ("the '791 patent") would have expired on March 4, 2001. However, because the Federal Circuit Court of Appeals affirmed on February 13, 2001, this Court's finding that Andrx's generic product did not infringe the '791 patent, Andrx's generic product would have been eligible for approval that same day. See Biovail Corp. International v. Andrx Pharmaceuticals, Inc., No. 00-1260, 2001 WL 118289 (Fed. Cir. February 13, 2001).

9. Federal defendants do not dispute the first two sentences of paragraph 9 but lack sufficient knowledge to form a belief concerning the filing of a provisional application on May 1, 1997.

10. Federal defendants do not dispute the first sentence of paragraph 10 but lack sufficient knowledge concerning the date when Biovail publically disclosed the listing of the '463 patent.

11. Paragraph 11 is a legal argument to which no factual response is required.

Respectfully submitted,

STUART E. SCHIFFER
Acting Assistant Attorney General

GUY A. LEWIS
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By: BARBARA PETRAS
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March 29, 2001

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

ANDRX PHARMACEUTICALS, INC., Plaintiff, v. BIOVAIL CORPORATION INTERNATIONAL, Defendant, and TOMMY G. THOMPSON, Secretary, U.S. Department of Health and Human Services, BERNARD A. SCHWETZ, D.V.M., PhD., Acting Principal Deputy Commissioner, U.S. Food and Drug Administration, and U.S. FOOD AND DRUG ADMINISTRATION, Additional Defendants.	Case No. 01-6194-CV-DIMITROULEAS

MEMORANDUM OF FEDERAL DEFENDANTS IN OPPOSITION TO PLAINTIFF'S MOTION FOR PARTIAL SUMMARY JUDGMENT AND IN SUPPORT OF MOTION TO DISMISS AMENDED COMPLAINT

In its Omnibus Order of March 6, 2001, this Court granted the federal defendants an extension of time until March 30, 2001, to respond to Andrx's motion for partial summary judgment and to make any changes to their pending motion to dismiss. Subsequently, on March 16, 2001, Andrx amended its complaint. The complaint, as amended, however, still fails to state an actionable claim against the federal defendants and fails to allege a justiciable case or controversy with respect to these defendants sufficient to invoke the Court's jurisdiction. Accordingly, the amended complaint should be dismissed as to the federal defendants.

In addition, although federal defendants take no position on Andrx's motion for partial summary judgment to the extent it challenges Biovail's actions or seeks relief against Biovail, Count I of Andrx's complaint also seeks a declaration that "Biovail's improper listing of the '463 patent does not constitute a basis for the FDA to withhold final approval of Andrx's ANDA No. 75-401." Amended Complaint ¶ 76. In fact, however, FDA is statutorily precluded from approving Andrx's ANDA pending completion of the patent dispute process set forth in the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act ("FDC Act"). Accordingly, Andrx is not entitled to the declaratory relief it seeks as a matter of law. The federal defendants therefore oppose summary judgment on Count I of Andrx's amended complaint to the extent it improperly seeks declaratory relief challenging FDA's refusal to approve Andrx's ANDA.

FACTUAL BACKGROUND

As this Court is aware, Biovail revealed for the first time, in a pleading filed on February 26, 2001, that it had made manufacturing changes to Tiazac. See Biovail's Memorandum in Opposition to Plaintiff's Motion for Expedited Treatment and a Preliminary Injunction. Specifically, Biovail stated that it had recently revised its manufacturing process for Tiazac so that 1.1 percent (by weight) of the diltiazem hydrochloride, the active ingredient, is now outside the coated beads within each capsule. Id. at 3-4; Declaration of Paul Maes at ¶¶ 4, 5. Biovail further asserted in its pleadings that the NDA for Tiazac is "broad enough to cover *both* versions of the product, *i.e.*, whether produced using the old manufacturing method or the new one" and that Biovail would advise FDA of this change in its next annual report. See Biovail Memorandum at 4; Maes Declaration at ¶¶ 6, 7; Declaration of John R. Markus at ¶ 6.

After considering the arguments and new information presented by Biovail in its

memorandum and supporting declarations, the federal defendants felt it necessary to submit to the Court a Notice of Change in Position ("FDA Notice"). In that Notice, submitted on February 28, 2001, shortly before this Court held argument on plaintiff's motion for preliminary injunction, the federal defendants advised the Court of FDA's belief that "the changes in formulation and manufacturing of Tiazac® described by Biovail are not in fact covered by the approved NDA for Tiazac®." FDA Notice at 3. As a result, FDA had "preliminarily concluded that Biovail must file a supplement to its NDA for agency approval before it can distribute the drug product with the revised manufacturing processes and new formulation" Id. The FDA further stated that "it now appears from Biovail's newly submitted declarations that the '463 drug patent does not claim the drug product as originally approved, but only claims the product in its revised (and unapproved) form." Id. The agency thus advised the Court that, "by virtue of Biovail's own statements, FDA is now of the view that the '463 patent does not claim the approved drug product as required by the statute and therefore cannot be listed in the Orange Book for Tiazac®." Id. FDA noted, however, that it had "deferred taking any further action with respect to the '463 patent so as not to interfere with the Court's consideration of this issue and in order to permit all parties to be heard." Id. at 4.

At the hearing on March 1, 2001, this Court asked counsel for the federal defendants how the FDA would normally handle the information newly disclosed by Biovail if this litigation were not pending. See Transcript of Hearing at 5 (excerpts attached hereto as Exhibit A). Counsel indicated to the Court that FDA "would be seriously considering delisting the patent," but that the agency "might first seek more information from Biovail." Id. Counsel further indicated that, while the agency would have been justified had it simply decided to delist the '463 patent, "the agency felt that it would be more prudent to await this hearing and see what

develops, rather than taking unilateral action on its own." Id. Subsequently, when pressed further by the Court, counsel stated that, if there were no lawsuit pending, the agency "would be prepared to act" – either by "immediately delisting the patent or more likely seeking a little bit more information . . . . Probably the latter." Id. at 6-7.

Subsequently, on March 6, 2001, this Court denied Andrx's motion for a preliminary injunction for lack of subject matter jurisdiction. Immediately thereafter, by letter dated March 7, 2001, Biovail requested an opportunity to meet with FDA to present information about what it described as "a minor manufacturing change related to the production of its Tiazac." Letter from John B. Dubeck (attached hereto as Exhibit B). FDA agreed to this request by letter dated March 14, 2001 (attached hereto as Exhibit C), and requested that Biovail submit any additional relevant information concerning the Tiazac manufacturing and formulation changes to the agency prior to the meeting. Letter from Dr. Raymond J. Lipicky, M.D. (March 14, 2001). Biovail submitted its additional material on March 19, 2001, and agency officials met with Biovail officials on March 20, 2001. At the meeting, Biovail described the manufacturing and resulting formulation changes it had implemented for Tiazac and argued that the approved NDA for Tiazac covered those changes.

After reviewing the materials Biovail had submitted to the agency and considering the information presented at the meeting, FDA informed Biovail by letter dated March 23, 2001 (attached hereto as Exhibit D), that, contrary to Biovail's assertions, the approved drug application for Tiazac does not in fact provide for the manufacturing changes that Biovail had made. Letter from Dr. Raymond J. Lipicky, M.D. (March 23, 2001). The agency noted that Biovail's manufacturing changes resulted in 1.1% of free diltiazem, the active ingredient in the product, being available for immediate release, whereas the approved drug product does not

contain any intended amounts of free diltiazem. Id. at 2. As a result, the agency explained, "the drug product resulting from this manufacturing change is not your approved diltiazem drug product." Id. FDA also determined that the manufacturing change that Biovail had implemented constituted a "major" change under the FDC Act, 21 U.S.C. § 356(a)(c)(2), because "it results in a change in the formulation of the product and it may affect the controlled release of the product." Id. The agency thus concluded that Biovail would be required, pursuant to 21 U.S.C. § 356(a)(c)(1), to submit a supplement for FDA approval before it could lawfully begin marketing the newly formulated drug product. Id. at 1-2.

Upon concluding that Biovail's Tiazac NDA does not encompass the manufacturing changes described by Biovail in its court pleadings and submissions to the agency, FDA then requested, by letter dated March 23, 2001, that Biovail determine whether the '463 patent "covers the approved Tiazac drug product, which contains diltiazem hydrochloride only in time-release coated beads." Letter from Ralph Lillie (attached hereto as Exhibit E). The agency explained that, if Biovail determined that the '463 patent covers the approved drug product, then Biovail would be required to submit a signed declaration to that effect by 5:00 p.m. on March 26, 2001. Id. at 3. FDA further advised Biovail that, if it failed to submit an appropriate declaration by that time, the agency would consider Biovail to have withdrawn its original certification to the '463 patent. Id. In such event, FDA would have then delisted the patent.

On March 26, 2001, in response to FDA's letters clarifying the identity of the approved Tiazac drug product and requesting that Biovail determine whether the '463 patent covers the product as approved, Biovail submitted to FDA, in the form requested by the agency, a declaration stating: "The undersigned declares that Patent No. 6,162,463 covers the formulation, composition, and/or method of use of Tiazac. This product is currently approved under section

505 of the Federal Food, Drug, and Cosmetic Act." See Letter and Declaration of Eugene Melnyk (attached hereto as Exhibit F). As a result of Biovail's submission of this declaration affirming that the '463 patent covers the currently approved Tiazac product, FDA has not withdrawn the patent listing from the Orange Book.

ARGUMENT

I. Andrx's Amended Complaint Should Be Dismissed as to the Federal Defendants

In its amended complaint, Andrx identifies federal defendants Thompson, Schwetz, and the FDA as "additional defendants" and states that they are named "for the purpose of ensuring that Andrx is able to secure complete relief against defendant Biovail, including making such discovery as the Court directs, and to the extent these defendants are responsible for the implementation of any interpretation, declaration or order made in this action." Amended Complaint ¶ 9. Despite this disclaimer, however, Andrx's amended complaint seeks declaratory relief effectively challenging FDA's refusal to approve its ANDA for generic Tiazac. For instance, where the original complaint sought to enjoin FDA "from requiring Andrx to certify to the '463 patent or from delaying approval of Andrx's ANDA for any reason relating to the '463 patent," Complaint (Sixth Prayer for Relief), the amended complaint seeks a declaration that "Biovail's improper listing of the '463 patent does not constitute a basis for the FDA to withhold final approval of Andrx's ANDA No. 75-401." Amended Complaint ¶ 76 & Fourth Prayer for Relief. Andrx also alleges that "[t]he Hatch-Waxman Act, 21 U.S.C. § 355(j)(5)(B)(iii) does not authorize the FDA to delay approval of Andrx's ANDA based on Biovail's improper listing of the '463 patent," Amended Complaint ¶ 114, and seeks a declaration that "to the extent any litigation proceeds between Andrx and Biovail concerning whether Andrx's product infringes the '463 patent, no further delay in the FDA's approval of Andrx's ANDA is permitted under the

statute . . . ." Amended Complaint (Tenth Prayer for Relief).

Thus, even though Andrx's amended complaint no longer explicitly seeks injunctive relief against FDA, it nonetheless seeks declaratory relief that would effectively require FDA to approve Andrx's ANDA.[1] Like the original complaint, however, Andrx's amended complaint is devoid of any allegation that, even if taken as true, would entitle Andrx to the declaratory relief it seeks with respect to the FDA. Although the amended complaint contains numerous allegations of wrongdoing on the part of Biovail, the complaint does not allege that FDA failed to comply with the FDC Act or any regulation, or that the agency's actions in listing the '463 patent and withholding final approval of Andrx's ANDA were otherwise arbitrary, capricious, or contrary to law. See 5 U.S.C. § 706. Absent such allegations, Andrx lacks any basis for sustaining an action against the federal defendants.

As discussed more fully in the previously filed Memorandum of Federal Defendants in Opposition to Plaintiff's Motion for Preliminary Injunction and in Support of Motion to Dismiss ("Opposition Memorandum"), which is incorporated herein by reference, Andrx cannot simply file suit against FDA officials and seek declaratory relief that would effectively compel agency action without basing its request upon some allegation that would entitle it to such relief. Under the circumstances, Andrx's complaint fails to allege a justiciable case or controversy with

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[1] Andrx also seeks an order "[d]irecting the federal defendants to comply with all orders and declarations made against Biovail in the manner acknowledged in their representations to the Court, and with respect to the Court's interpretation of the statutes, rules, and regulations at issue in this case." Amended Complaint (Fourteenth Prayer for Relief). As the federal defendants have previously pointed out, however, the appropriate course for remedying an improper patent listing is not the entry of declaratory or injunctive relief requiring FDA to delist the patent or approve the ANDA despite the patent listing, but for the court, upon the resolution of private litigation between the affected parties, to order the patent holder to request that FDA remove the patent from the Orange Book. Once the patent holder makes such a request of FDA, the agency will delist the patent. No court order against FDA is necessary in such circumstances.

respect to the federal defendants and fails to state a claim upon which relief can be granted against these defendants. Accordingly, the complaint should be dismissed as to the federal defendants pursuant to Fed. R. Civ. P. 12(b)(1) and 12(b)(6).

II. Andrx's Motion for Partial Summary Judgment Should be Denied to the Extent It Seeks Declaratory Relief Against the Federal Defendants

Even if Andrx's amended complaint stated a claim against the federal defendants, Andrx is not entitled to the declaratory relief it seeks against the federal defendants as a matter of law. Count I of the amended complaint, upon which Andrx seeks summary judgment, alleges, among other things, that Biovail's listing of the '463 patent is "in blatant violation of the Hatch-Waxman Act," and seeks injunctive relief requiring Biovail to immediately delist the patent. Amended Complaint ¶¶ 71, 76. As noted above, however, this Count also requests a declaration that "Biovail's improper listing of the '463 patent does not constitute a basis for the FDA to withhold final approval of Andrx's ANDA No. 75-401." Id. at ¶ 76.

Although federal defendants take no position on Andrx's motion for partial summary judgment to the extent it challenges Biovail's actions or seeks relief against Biovail, the Court should deny Andrx's motion to the extent it seeks declaratory relief challenging FDA's failure to give final approval to Andrx's ANDA. Indeed, under the clear terms of the Hatch-Waxman Amendments, FDA is statutorily precluded from giving final approval to Andrx's ANDA unless and until either the patent is delisted or the procedures set forth in the statute for resolving patent disputes have run their course. As explained more fully in the federal defendants' initial opposition memorandum, the FDC Act, 21 U.S.C. § 355(j)(2)(a)(vii), requires an ANDA to include a certification with respect to each patent which claims the listed drug. When an ANDA makes a so-called paragraph IV certification stating that the patent is invalid or will not be

infringed, the agency is then prohibited from approving the ANDA until the expiration of 45 days from the date the generic firm provides notice to the patent holder of its certification. See 21 U.S.C. §§ 355(j)(2)(a)(vii)(IV); 355(j)(5)(B)(iii).[2] If the patent holder brings a suit for patent infringement within the 45-day time period, then the approval cannot be made effective before the conclusion of that litigation or the expiration of a 30-month period, whichever occurs earlier, unless the court hearing the infringement action shortens the period due to a party's failure to reasonably cooperate in expediting the action. See id.

Under these circumstances, the declaration Andrx seeks in Count I of its amended complaint is at odds with the clear provisions of the statute. Simply put, Biovail's listing of the '463 patent – even if improper as Andrx has alleged – nevertheless poses at least a temporary statutory bar to final approval of Andrx's ANDA. Unless and until the patent is delisted from the Orange Book or the Hatch-Waxman patent dispute procedures have run their course, FDA is statutorily precluded from approving Andrx's ANDA. Thus, to the extent Andrx seeks declaratory relief that would effectively compel the approval of its ANDA despite the continued listing of the '463 patent, Andrx is not entitled to such relief as a matter of law and its motion for partial summary judgment must therefore be denied.

III. FDA's Actions In Listing the '463 Patent and Maintaining the Listing Were Reasonable

Finally, to the extent Andrx's declaratory claims in Count I can be construed to implicitly challenge FDA's initial listing of the '463 patent, or its continued listing, Andrx has failed to show as a matter of law that FDA's actions were arbitrary, capricious, not in accordance with law, or unwarranted by the facts. See 5 U.S.C. § 706; Florida Manufactured Housing Ass'n Inc.

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[2] Andrx made its paragraph IV certification with respect to the '463 patent on February 21, 2001.

v. Cisneros, 53 F.3d 1565, 1572 (11th Cir. 1995). As explained in the federal defendants' initial opposition memorandum, FDA's listing of the '463 patent was a reasonable exercise of its limited ministerial role in the patent listing process as set forth in the statute and regulations. Opposition Memorandum at 12-16. FDA's subsequent decision to maintain the listing, after clarifying the identity of the approved drug and receiving Biovail's affirmation that the patent claims the approved drug, was likewise reasonable and consistent with the agency's ministerial role.

In this case, it became evident from the representations in Biovail's pleadings that Biovail's proffered justification for listing the '463 patent with FDA was based upon a misapprehension concerning the identity of the "approved" drug product. Under the circumstances, FDA deemed it appropriate and necessary to clarify the proper identity of the drug product for the benefit of the parties and the Court. After careful consideration of all the evidence submitted by Biovail, FDA determined that the approved Tiazac drug product did not encompass the manufacturing and formulation changes that Biovail had implemented. This decision is clearly within FDA's expertise and entitled to substantial deference. See Florida Manufactured Housing Association, Inc., 53 F.3d at 1572 (11th Cir. 1995).

Having thus clarified the identity of the approved drug product, it was reasonable for the agency to then provide Biovail with an opportunity to determine whether the '463 patent claims the approved product and, if so, to make an appropriate certification to that effect to the agency. In so doing, FDA acted pursuant to the provisions of the statute and regulations, which require that the agency list patents in the Orange Book upon the patent holder's certification that the

patent satisfies the statutory standard.[3] See 21 §§ 355(b)(1); 355(c)(2); 21 C.F.R. § 314.53. However, in carrying out its ministerial function, FDA did not ignore the circumstances of this case. Indeed, in its letter to Biovail, FDA made clear that it would consider the patent withdrawn if Biovail failed to promptly submit the necessary certification with respect to the approved drug product. See Lillie Letter (Exhibit E).

Had Biovail not recertified as requested, FDA was prepared to delist the patent based upon the representations Biovail had made in its pleadings, which at least suggested that the '463 patent only claimed Tiazac to the extent it had been reformulated, and not in its original, approved formulation. However, Biovail never explicitly stated that the '463 patent did not claim the drug in its original formulation and, when given the opportunity to so state by FDA, the company submitted a signed declaration affirming that the '463 patent claims the currently approved drug product. Under these circumstances, it was plainly reasonable for FDA, once it had determined the proper identity of the "approved" drug product, to extend to Biovail the opportunity to clarify whether the patent claimed the "approved" product. It was equally reasonable for FDA, upon receipt of such clarification, to rely on Biovail's signed declaration and maintain the patent listing rather than looking beyond the face of the declaration and attempting to engage in its own independent construction of the patent claim, a process for which the agency lacks both the expertise and the resources. Thus, FDA's actions in both listing

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[3] FDA's approach here is consistent with the agency's position in Pfizer v. FDA, 753 F. Supp. 171 (D. Md. 1990), a case in which Pfizer, unlike Biovail, did not submit a declaration certifying that the patent at issue claimed the approved drug product. In that case, the approved drug product, for which Pfizer had two patents listed, was a nifedipine capsule. Pfizer subsequently sought to submit a third patent for a nifedipine tablet. FDA refused to list the patent because, as Pfizer itself acknowledged, the patent claimed only the tablet form of the drug and not the approved capsule. Pfizer v. FDA, 753 F. Supp. at 174-75.

the '463 patent and in maintaining that listing, were reasonable and in accordance with statutory command.

CONCLUSION

For the foregoing reasons, Andrx's motion for partial summary judgment should be denied and the federal defendants' motion to dismiss should be granted.

Respectfully submitted,

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