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ASSESSING THE IMPACT OF A SAFE AND EQUITABLE BIOSIMILAR POLICY IN THE UNITED STATES

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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ASSESSING THE IMPACT OF A SAFE AND EQUITABLE BIOSIMILAR POLICY IN THE UNITED STATES

WEDNESDAY, MAY 2, 2007

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

The subcommittee met, pursuant to call, at 10:05 a.m., in room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. (chairman) presiding.

Members present: Representatives Pallone, Waxman, Gordon, Eshoo, Green, DeGette, Capps, Allen, Baldwin, Schakowsky, Solis, Hooley, Matheson, Dingell, Deal, Wilson, Pitts, Ferguson, Rogers, Myrick, Sullivan, Murphy, Burgess, Blackburn, and Barton.

Also present: Representative Inslee.

Staff present: Jack Maniko, John Ford, Bobby Clark, Virgil Miller, Lauren Bloomberg, Melissa Sidman, Jesse Levine, Nandan Kenkermath, Chad Grant, and Ryan Long.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. This hearing is called to order. Today the subcommittee is meeting to hear about assessing the impact of a safe and equitable biosimilar policy in the United States. Needless to say, the topic of today's hearing is of great importance and has generated a lot of interest over the past few months. Recent advancements in science have resulted in a new class of innovative medicines commonly referred to as biologics. These biotech drugs are complex molecules that are typically derived from living organisms which are designed to treat a number of chronic and often debilitating diseases. While older versions of these products have existed for many years, manufacturers have made great strides in developing a broader range of biologic products that treat a greater number of conditions and illnesses. Diabetes, cancer, heart disease, multiple sclerosis are among a range of devastating illnesses for which there are now new treatments because of improvements in the research and development of biologics. As a result, these life-saving and life-enhancing therapies have given patients and their families a renewed sense of hope for a longer and better life.

Because of the great promise biologics hold, they are one of the fastest-growing components of the pharmaceutical market. Unfor-

tunately, however, they are one of the most expensive. The price of a biologic can be substantial as well as prohibitive. Take insulin, for example. It was noted in a recent New York Times article that the drug cost State Medicaid programs $500 million in 2005. Furthermore, people who suffer from diabetes in this country, as well as Government and private insurers, spend a combined $3.3 billion a year on insulin. Researchers have suggested, however that the price of insulin might drop 25 percent if generic or follow-on versions were made available. The savings would accrue to many, including patients, employers, and insurers. Competition from generic versions of chemical drugs have proven to be an effective way to help lower healthcare costs. As we all know, a generic drug can cost 30 percent to 80 percent less than its equivalent brand-name drug. In 2005, the average prescription filled with a brand-name product cost $95.54. The average cost for a generic filled with a generic drug was $28.71, and that is a savings of nearly $70 on the average prescription.

We need to apply what we learn from generic versions of chemical drugs and biologic products so that we can produce measurable savings. That is what I believe that Mr. Waxman has attempted to, with introduction of his legislation. He has introduced a bill called the "Access to Lifesaving Medicine Act" of which I am a co-sponsor. In 1984, you all know that Mr. Waxman paved the way for safe and affordable generic drugs to enter the market easily, and we were still preserving incentives for brand-name companies to develop new and innovative therapies. As we search for a way to lower costs and preserve innovation with biologics, Mr. Waxman is once again an authoritative voice in this debate, and I thank him for directing our attention to this important issue. Thank you, Henry.

Congress, I believe, needs to approve a pathway for generic biologics to be brought to the market, and this will be a priority for our subcommittee. I know many of my other committee members, and I will mention Mr. Inslee, Mr. Green, Ms. Baldwin, Ms. Eshoo, and others have also indicated their eagerness to address this important issue; and I am looking forward to gathering their input as we move forward as well.

While I am a co-sponsor of the Access to Lifesaving Medicine Act, I will be the first to admit that the legislation is not without controversy. Over the course of the past few months, I have heard from numerous stakeholders on this issue and believe that each side has its own merits. Several questions continue to arise. What level of science will be used to determine comparability standards for these new products? What amount of science should be used to determine interchangeability? Who should make such determinations? Should it be Congress or the expert agency that we have typically charged with the regulation of drugs and biologics? How do we preserve innovation while achieving price competition? And how do we strike a balance between protecting intellectual property but ensure that generic versions of biologics are approved and enter the market in a timely manner. These are some of the questions whose answers will shape the debate and help us determine how the FDA approves safe and effective generic or follow-on versions of biologic products.

I just want to thank all of our witnesses for being here today. You represent the experts in the field and will tell you that the members of the subcommittee are eager to hear what you have to say and ask questions of you, so thank you for being here and I am certain that today's hearing will be extremely informative for all of us.

Mr. Deal will be here soon, so I will now introduce the gentleman from Michigan, Mr. Rogers.

OPENING STATEMENT OF HON. MIKE ROGERS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. ROGERS. Thank you, Mr. Chairman. I will be brief. I am looking forward to the testimony.

I do get concerned about the direction we take. The average biologic takes about 15 years in development, $1.2 billion to develop. And the harder we make it for people to go through that process, or at least some degree of certainty to recoup their losses and their investment, it concerns me greatly. I am not sure that we are going to insert any great innovation to cheaper and better and quality drugs.

My other great concern in the bill is that we haven't really addressed the security issue. A lot of these biologics now are using twin-strand therapeutic issues. Bryson, abrin, viscumin, things that were highly regulated by the FDA; and if we had to throw this open, I get very, very concerned about how we keep and maintain the safety and security of those particular agents when developing these biologics.

So I have a lot of questions today, and I look forward to the debate and I know all our intentions are good; and hopefully at the end of the day, we will do no harm before we seek to do any good.

Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you, and I recognize Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman, for calling this hearing today.

Biotech drugs, also known as biologics, have emerged as one of the fastest-growing categories of drugs. Some of these medicines are literally lifesavers for people with a host of serious diseases, but these products are also among the most expensive medications for U.S. consumers. Patients who need these drugs often have to pay hundreds of thousands of dollars a year for them. Although it is true many people have insurance to cover the cost of these drugs, those who have 20 percent co-pays still owe thousands of dollars a year, and it is obviously a very serious problem for the 47 million uninsured. They have to pay the whole price. More likely than not, they go without the lifesaving drugs.

The rapidly escalating cost of biotech drugs will have drastic consequences for the healthcare system. These medicines are steadily driving up the cost of Medicare, Medicaid, and health insurance overall. This is a burden that cannot be sustained. The Federal

Government will be hard pressed to afford it. The private sector is already pleading for relief.

I have long believed that marketplace competition is the best way to bring down drug prices, but unless the FDA is given the clear, legal authority to approve copies of biologics, there will be no generic competition for biotech drugs, leaving employers, insurers, and the Federal Government to pay the staggering monopoly prices we have today.

Earlier this year, Mr. Chairman, you and I and some of our colleagues introduced the Access to Lifesaving Medicines Act. This bill ensures only safe and effective biologics will be approved. It gives FDA complete discretion to require a full complement of testing, including clinical testing on the product, if FDA believes that is necessary to require tests. If FDA does not believe it is necessary is only another way to delay generic competition.

There are a lot of issues to be discussed here, patient safety, intellectual property rights, the incentives for innovation to name a few; but I would like to note that since we first introduced this bill the debate on these issues has dramatically changed. At first the opposition claimed there should not be an abbreviated pathway for generic biologics at all. Now, the question that everyone is asking, even the opposition, is not if but how to establish a pathway. It is important to note there is a very broad base of support for this legislation. There is currently a wide-ranging coalition of over 40 consumer groups, health plans, and businesses who have endorsed the bill. With so many supporters of the bill, we had some hard decisions about our witnesses today and we obviously could not have all of them present. So I would like to ask unanimous consent to add to the printed record the written statements of some of these groups that could not be here today. I have statements from the AARP, the Coalition for Competitive Pharmaceutical Marketplace, the California Public Employees Retirement System, and the AFL-CIO.

These and many other groups all recognize that the time to move forward with establishing an abbreviated pathway is now. Opponents have attempted to attack the bill by arguing competition will only lower prices by a small amount. Well, even a small amount could bring in billions of dollars of savings. We have to find a way to introduce competition into this market. We need that balance that we tried to achieve in 1984, and we were successful at doing it, giving incentives for development of new products but bringing about the benefits of competition in the marketplace. Too often we hear now, as we heard in the mid–1980's, we need all the incentives. Give us a permanent monopoly. Don't provide competition, these competitors are not as good, they can't be as safe. Well, let us look a little bit more skeptically because those were the arguments we heard then. They were wrong then and they are wrong now. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Waxman. Without objection we will introduce those statements into the record.

Mr. DEAL. Mr. Chairman, could I ask unanimous consent that others might introduce similar-type comments on this, any other member of the committee?

Mr. PALLONE. Absolutely.

I will recognize the ranking member.

OPENING STATEMENT OF HON. NATHAN DEAL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. DEAL. Thank you, Mr. Chairman. This morning's hearing addresses an exciting and changing realm of the pharmaceutical industry. The biologic pharmaceutical market has grown dramatically in recent years, and the FDA has steadily approved new biologic medications. Growth in this market is only forecast to increase in the future. I am sure most members at this point understand that biologics have a greater complexity than traditional drugs, and there is not an appropriate pathway at the FDA for follow-on protein products. I would hope this hearing would help guide the committee to inform us about what framework would be suitable for the approval of follow-on products in a manner that assures patient safety because for me, that is the heart of this issue.

I realize there are varying opinions along this line. Some contend legislation ought to mandate clinical trials while others feel this determination should be left to the FDA. Certainly we must ensure the FDA has the tools to approve safe and effective medications and allow them to use their discretion and expertise when evaluating follow-on product applications.

We also ought to act in a way that will adapt to the changes and signs in the field of biotechnology in the coming years. While the Hatch-Waxman Act was passed over 20 years ago, legislation has largely stood the test of time and provided a workable solution to get low-cost generic products to consumers. As the biologic drug market continues to grow and the science advances, legislation should be able to accommodate those changes, not hinder them, recognizing that while the science may not be there today, it could be tomorrow.

One of the most difficult aspects of this issue is to provide a balance between incentives for innovation while allowing similar lower-cost products to come to market. Hatch-Waxman provides these incentives for innovation in the form of market exclusivity and patent term restoration. As we strike this balance, I believe we do need to provide some period of market exclusivity as an incentive for innovation while ensuring that the judicial process and patent litigation can be resolved in a fair and timely manner. Other countries are already acting on this issue, and the Congress needs to provide a pathway for the approval of follow-on biologics in this country. We have an opportunity to provide patients access to a lower cost alternative for their needed medications. While the fund is unclear, the degree of savings that could be achieved with a follow-on protein product for status quo is no longer acceptable and ignores the possibilities presented by generic biologics. By no means does the committee face an easy task. This is a complex subject, and we must wrestle with a number of scientific, regulatory, intellectual property, and safety issues. However, I do believe we can resolve and balance these issues in order to provide patients' access to safe, lower-cost medications.

Thank you, Mr. Chairman. I will yield back my time.

Mr. PALLONE. Thank you. I recognize our vice chair, Mr. Green.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman, for holding the hearing on follow-up biologics and the issues we must consider for developing a pathway for regulatory approval of biosimilars. This extremely complex issue and whatever way we resolve it will have significant implications for employers, innovators, generic industry, and most importantly, the patients who depend on these life-improving and lifesaving therapies. There is no question we have to get this right, and this hearing represents a good first step toward the goal by giving Members a chance to dig deeper into this issue and weigh the risk and benefits of any movement forward on biosimilars.

I think we can agree that there needs to be the regulatory pathway in this country to follow-on biologics. Canada, the European Union, and Australia each put in place pathways for the approval of follow-on biologics.

We have also recognized the undeniable fact that biologics are very different from small molecule drugs and present unique concerns about safety and effectiveness. Unlike small molecule drugs, biologics are created using living cells that are intended to imitate proteins that will naturally occur in the body if the patient were healthy. The time and expense that goes into making biologics is much greater than the process of manufacturing a small molecule drug. So it is no surprise that these therapies are quite expensive for consumers and purchasers. I share the goal of lowering patients' cost of a follow-on pathway but not at the expense of those same patients' safety and not if it results in stifling the innovation that would produce new, more effective therapies and potentially a cure for the incurable diseases we see too many of our family members and neighbors fight day in and day out.

The issue of drug safety is at the heart of this debate and the primary reason why I co-sponsored the legislation sponsored by my colleague from Washington, Jay Inslee. We all seem to come to the same conclusion that an exact replica of a biologic product cannot be made. The questions remain what effect does a small change in the amino acid sequence produce and is that effect large enough and concerning enough to warrant additional clinical trials before the follow-on biologic is available to the public? Can we in good conscience consider these follow-on drugs safe if they have never been tested on a human population? Several of my colleagues will certainly reply that the FDA is equipped to make that decision on a case-by-case basis and that we shouldn't be legislating science. I have no doubt the FDA has top-rate scientists on its payroll and are more than capable of making these decisions. But it would be disingenuous for us to point to the Vioxx and Ketek and why we need drug safety reform at FDA and in the next breath give FDA carte blanche authority to approve any follow-in biologic without some sort of clinical trials for safety and effectiveness.

We also need to make sure we don't cut off our nose to spite our face in this debate. Biologics offer tremendous promise in the treatment of disease, but there are too many patients out there waiting for the improved treatment or cure that can only be achieved through innovation. My concern is we will rush to facilitate copies

of old therapies at the expense of new therapies. Any action by this committee is to balance the desire to lower the cost of biologics with the need to preserve the incentives for innovation so that more Americans can benefit from the therapeutic promise of biologic products.

Mr. Chairman, I hope the committee will keep this delicate policy balance at the forefront of the debate as we move forward, and again, I would like to thank our witnesses for appearing today; and I yield back my time.

Mr. PALLONE. Thank you. I recognize my colleague from New Jersey, Mr. Ferguson.

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

Mr. FERGUSON. Thank you, Mr. Chairman, and thank you for holding this hearing.

The creation of a pathway for the approval of follow-on biologics is really a tremendous opportunity, and it has to be done with a great deal of thought and with thorough consideration for all of the potential risks and benefits that might come with such a pathway; and it has to be done with obviously a great deal of scrutiny and a great deal of thoughtfulness.

It is a great opportunity but is one that has to provide the framework to ensure that the public is not placed in danger by being exposed to replicas of these complex biologics that haven't been thoroughly vetted for safety. We must ensure that the approval of follow-on biologics is based on the same rigorous standards of safety and purity and potency that is applied by the FDA for the approval of the original biological product. I think common sense would dictate that.

Clinical trial data and evidence are vital for establishing the safety and efficacy of highly complex biologic products. Testing has to be done to avoid putting patients at risk for effects of an adverse immune system response. In addition to safety, we also have to handle this opportunity correctly so as not to risk the development of future lifesaving therapies. We must include proper protections to foster innovation and further secure our position as the world's medicine chest, leading the world of lifesaving therapies to humanity's most horrific diseases. The creation of a pathway for approval to follow-on biologics is laudable, but we should not rush to create a pathway while being blinded by potential savings from follow-ons. We shouldn't rush to save a buck and put people's lives in danger.

A recent analysis from the healthcare research firm, Avalare, finds that follow-on biologics will save about $3.6 billion over 10 years. Now, $3.6 billion is a lot of money. It is considerable, but we have to ask the question of what is the cost of those savings?

Mr. Chairman, we have a great opportunity but also a tremendous responsibility. Today is the first step toward taking on that responsibility and taking advantage of this opportunity. I look forward to working with you and the others on this committee to make sure that we get this right. And I yield back.

Mr. PALLONE. Thank you. I now recognize the chairman of our full committee, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Chairman DINGELL. Thank you for holding this hearing. It is important. We are here to discuss the anticipated impact of a safe and equitable biosimilar policy in the United States. When the Congress granted the Food and Drug Administration the authority to approve generic versions of pharmaceuticals in 1984, we could not have foreseen the need for a similar pathway for generic biologics. Since then, the biotechnology industry has grown tremendously, and a number of biological products are on the market, treating a variety of medical conditions including life-threatening illnesses such as cancer, multiple sclerosis, diabetes, and HIV/AIDS. In some instances, these biological products are the only available therapy. In others, biotechnology represents a clear clinical advantage over all other available therapies. As this industry continues to discover potentially lifesaving therapies, more patients will depend on these products. Unfortunately, not all patients can afford these needed therapies and must therefore forego needed treatments. We must find a way to ensure greater access as this science progresses. There is broad agreement that we should create a pathway for biosimilars.

As we explore this idea, it is necessary that our solutions are grounded in science and fair to consumers. Innovators as well need financial stability to sustain their research into groundbreaking therapies. One issue that confronts us now as policymakers is the science behind biosimilars. What standards will ensure that the generic biologics are as safe as the original products? How will they function in the human body? Should clinical trials be required for approval of biosimilars? Can a generic product be created that is genuinely interchangeable? Can and should a manufacturer of a biosimilar product duplicate the innovator's manufacturing process to avoid potentially adverse reactions? Patients' safety must be our guiding principle in searching for an appropriate pathway.

I am pleased that this hearing is being held today. I look forward to the testimony of our witnesses as well as the input of our members. It is my intention to work with my colleagues on the committee to craft a sensible and fair biosimilar policy and to work with my colleagues to achieve this goal in the 110th Congress. Your efforts this morning, Mr. Chairman, and this hearing is a very important part of our effort in that regard. Thank you.

Mr. PALLONE. Thank you, Chairman Dingell. Mr. Murphy.

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

Mr. MURPHY. Thank you, Mr. Chairman. This hearing again points out the cycle of the issues Congress must deal with. We want medications that will save our lives, enhance our lives, and also treat disease. In order to do that, we need research and development work which costs billions of dollars. Clinical trials must be

undertaken in a scientifically balanced and reliable fashion, that we want Government agencies such as the FDA to review them carefully to test the products while they are trying to balance the pressure to get drugs to the public and the market in order to save lives and treat disease but at the same time having pressure on them to make sure they test them for all the safety factors. All this comes in the context of the public's call for affordable drugs because what good is a drug to treat a disease if you can only window-shop that medication and cannot really use it.

And so we are here dealing with the issue of generic or biosimilars, to cut costs to provide some market competition, to drive costs down, but make sure that the companies have enough money left at the end for their research and development which, of course, takes us back to the beginning of this whole cycle. It is a matter that Congress constantly must deal with that is an important part of our role here. The issues that we must deal with in any of these bills that deal with biosimilar drugs is to make sure that we do have portions in them that drugs do not get to market unless thorough testing is part of that and to make sure throughout this whole process that we are dealing with safety, affordability, and continuing on ways that maintain the research track which has given us so many medications which have saved our lives.

In all of this, I hope we continue to focus on patients as we move through healthcare issues such as these that emphasize patient quality, patient safety, and patient choice. These biosimilar drugs would provide all three of those if we do this right. So I am looking forward to the comments from the panelists today.

Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you. And now I recognize the gentlewoman from Colorado.

Ms. DEGETTE. Mr. Chairman, I think we all have the same goals of finding the balance, and I am looking forward to hearing the testimony so I will waive my opening statement.

Mr. PALLONE. Thank you. The gentlewoman from Tennessee.

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

Mrs. BLACKBURN. Thank you, Mr. Chairman. I do want to thank you for holding the hearing and to our witnesses that will be with us today.

We have all talked about the complex issue that follow-on biologic medications present because they are similar, because they are not identical like a generic drug; and so we do have to carefully consider the standards for approval, the potential of risk that are in that approval pathway.

When the healthcare costs are skyrocketing, and we hear this every time we come in for a committee hearing, we know that people are looking for new options for lowering drug costs; and we do know that patient safety has to be a priority. And Mr. Chairman, I hope that we will continue our discussion on this issue at another time and look at the intellectual property protections and infringe-

ments that may be there and the need for recognition of that as we view what is going to be a follow-on process.

We had the hearing a few weeks back with the FDA Commissioner von Eschenbach, and Ketek, the drug that is there to fight the bacterial infections, the side-effects that were there with the clinical trials, the problems that existed. So I think it is interesting that we are looking at a follow-on biologic approval pathway that would not require further safety testing.

So I am looking forward to the discussion today. I am looking forward to what we set as a pathway and hearing from our witnesses and having a discussion not only on the issue of safety which is before us today but also the scientific liability and legal consequences that may be a part of this process, and I yield back.

Mr. PALLONE. Thank you. The gentlewoman from California, Mrs. Capps.

OPENING STATEMENT OF HON. LOIS CAPPS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mrs. CAPPS. Thank you, Mr. Chairman. In 1984, Congress passed a bill that created a pathway for generic versions of traditional chemical drugs. It was a difficult and contentious time. But we have seen over the past 23 years how effective this has been on accessibility to medications and lowering drug prices, most importantly, providing continued incentives for drug innovation without compromising public safety.

So here we are in 2007 looking at a way to create a pathway for generic versions of biologic drugs, and we are now tasked with preserving the same goals of innovation and safety. Supporting innovative research into new lifesaving medications is vitally important. I know this especially because my State of California is such a world leader in biotechnology. I have been impressed with how important it is that we make sure to address patient protection and market exclusivity. However, it is extremely important also that we improve patients' ability to afford lifesaving medications. Quite frankly, with no competition on the markets, biologics remain out of economic reach for most of the people who need them.

I hope to hear today from witnesses on how we can balance innovation with patients' needs for cheaper, more accessible drugs. Just as for generic chemical drugs, generic biologics have the potential to reduce costs for consumers. But we also have to ensure that as we reduce drug prices, we maintain safety and effectiveness. Recent drug recalls highlight the importance of FDA's role in ensuring the safety of our drug supply. We can't stress this point enough. So I look forward to hearing about FDA's ability to assess follow-on biologic safety. Also, I hope to hear more about the FDA's capability to determine whether clinical trials may be necessary to determine if the drug is safe for the public and in what way they can be conducted. Scientific discovery has been moving at an astronomical pace, and we in Congress need to encourage it as much as possible. However, we also need to ensure that these discoveries reach those who would benefit from them and that the treatments are safe and effective.

I look forward to listening to today's witnesses as we explore this very important topic. And I yield back the balance of my time.

Mr. PALLONE. Thank you. Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. I will waive my opening statement and reserve time for questions.

Mr. PALLONE. Next we have Ms. Solis.

OPENING STATEMENT OF HON. HILDA L. SOLIS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. SOLIS. Thank you, Mr. Chairman. Thank you for holding this hearing today as we begin the discussion on whether FDA has the authority to approve similar versions of biologic medicines. I would like to thank my colleagues, Representatives Waxman, Inslee, Baldwin, and Green for their leadership on follow-on biologics or biosimilars. Recent scientific and technological advances have led to the development of biologic medicines which have great potential to address numerous diseases, including diabetes, cancers, HIV and AIDS, all of which affect many underserved communities, including the one which I represent.

The strides we have made in science are exciting. The manufacture of biologic medicines has the potential to save millions of lives, and biologics account for approximately $30 billion in sales. However, the cost of developing and manufacturing these biologics are extremely high; and the average cost of a 1-day supply of biologic medicines is $45. As a result, the cost for patients, insurers, private companies, and Government payers are quickly growing. And I am very concerned about the high cost of these medicines, especially the cost of those treatments for many who lack healthcare insurance or who are underinsured. We must strike a critical balance between patient safety and patient access to lifesaving medications.

I am committed to ensuring that all people have access to affordable medicines that are safe and effective. Despite the differences between chemical drugs and biologics, I believe that there is a way to provide patients with generic biologic medicines without compromising safety. The scientific experts at FDA should be allowed to have flexibility to determine what clinical tests are required, and we must find a balance to make sure that new medicines continue to be developed.

I look forward to hearing from our witnesses. I yield back the balance of my time.

Mr. PALLONE. Thank you. I now recognize the gentlewoman from New Mexico.

OPENING STATEMENT OF HON. HEATHER WILSON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW MEXICO

Mrs. WILSON. Thank you, Mr. Chairman, and thank you for having this hearing. I think we all recognize that there are some very difficult balances here. We all want a path or some kind of pathway for generic biologics. We are all concerned about safety, and of course we need to protect intellectual property rights and give predictability to investors so that we will allow and encourage continued innovation in the future.

And I think there is probably also general agreement that the certification process for saying that something is essentially iden-

tical is much more difficult in this case because we are talking about living organisms. We are not talking about a chemical compound. Products made from living tissue use proteins to change the course of a condition and have a therapeutic effect on a disease. This is very different from dealing with chemical compounds, and I think all of us recognize the very difficult balances we are going to have to strike here and what was difficult with the generic drug law, as my colleague from California mentioned, what was very difficult at that time will be multiplied tenfold in getting this right because the compounds are quite different and the legislation that addresses this will be a very difficult balance to strike.

Nonetheless, I commend the chairman and members of his committee for their determination to tackle this issue to see whether there is something we can do so that we create a pathway for generics that might be at less cost for a new class and a new kind of therapy in the area of medicine.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. I recognize the gentleman from Utah.

OPENING STATEMENT OF HON. JIM MATHESON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF UTAH

Mr. MATHESON. Thank you, Mr. Chairman. I think it is very important that we are talking on this issue, and I am pleased, Mr. Chairman, that you are conducting this hearing. I think this is a great opportunity for the legislative process to produce a good result because this is a complicated issue. There are some different pieces of legislation that have been introduced now that kind of lay down some different points of view on the issue. But my sense, having met with a number of stakeholders over the last few weeks about this, is that there is a reasonable solution; and if we work in a comprehensive and bipartisan way, I think that that reasonable solution will be attained and I think we can build consensus.

I look forward to participating in this hearing today and in the future hearings and being part of driving towards a reasonable solution.

With that, Mr. Chairman, I yield back the balance of my time.

Mr. PALLONE. Thank you and I now recognize our ranking member of the full committee, Mr. Barton.

Mr. BARTON. Thank you, Mr. Chairman. I will put my full statement into the record. I think this is an important hearing. It is a new subject and something that we need to get right, we need to get right on a bipartisan basis, and I look forward to the testimony and the work product that follows.

[The prepared statement of Mr. Barton follows:]

PREPARED STATEMENT OF HON. JOE BARTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. Chairman thank you for holding this hearing. The issue of follow-on biologic products has been the source of great debate.

This is an important, but very complex issue. Some have suggested rushing the legislative process and include follow-on biologic legislation on the reauthorization of the Prescription Drug User Fee Act. I think that this is an imprudent course of action and does a disservice to the deliberative nature of our committee. To do so will result in policy that is not fully vetted and the unintended consequences of our actions in this case could risk lives.

I believe it is important that the terminology we use this debate be accurate and precise. Generic biologics are not on the immediate horizon; the science just isn't there. Some have coined that term for use in this debate, but it not accurate and muddies the waters of our discussions. Generic denotes that the products are the same and can be freely substituted. Follow-on products are not the same and can have different characteristics that could result in different safety and efficacy profiles.

No one should have a patent in perpetuity. As we have seen with the Hatch-Waxman law of 1984, competition in pharmaceuticals can lead to lower prices without jeopardizing research and development into new products. follow-on biologic competition could be a good thing if done right. I believe we can and should create a pathway for follow-on biologic products to be approved without having to undergo the full blown biologics license application process. However, any abbreviated pathway must have two important elements.

First, we should not short-change safety in the interest of brevity. These are fundamentally different products. We will have two witnesses today who will testify to the science of these biologic products. The development of living organisms into a therapeutic treatment safe for humans is not an easy task and it is difficult top replicate. Most importantly, however, is that any minor modification to the sequencing of the properties of the product could have a profound effect on the safety profile of the product. For generic drug applications under section 505(j) of the Food, Drug, and Cosmetic Act, applicants are not required to undergo clinical tests to be granted approval. This can be done because the generic applicant is producing essentially the same product that is bioequivalent. Some have suggested that concept be translated to the approval of follow-on biologic products. Chemical and biologic products are truly apples and oranges, and we should not minimize these differences or complexities of the issues before us today.

I am looking forward to the testimony today that can shine some light on the true scientific and safety issues this committee should consider when drafting legislation to approve follow-on biologic products.

Ensuring safety is our utmost priority, but we must also consider the consequences our actions will have on the development of new drugs and cures that have yet to be discovered. Two weeks ago, we heard the testimony of Jim Thew, who suffers from Lou Gehrig's disease. Only one drug is available to treat this devastating disease, and that drug is over 10 years old. We cannot close the door to innovation because by doing so we will be closing the door to hope for the millions of Americans who want and need the next breakthrough therapy that will treat Lou Gehrig's, cancer, and a host of other diseases.

To protect innovation and medical progress we must protect the incentives necessary to induce investment in these areas. Allowing a follow-on to be approved a few short years after the innovator product may reap some short-term savings, but it will have a devastating impact on American companies' ability to produce new therapies. We can not be short-sighted in this debate. Like every other industry, intellectual property must be respected and protected. If it is not, we will see a dismantling of the biotechnology industry in this country, capital will find its way into other industries, and sick Americans will get sicker.

Again, it is important to note that we are not talking about products that are the same as we have for chemical drugs approved under the Food, Drug, and Cosmetic Act. These therapies are different and thus the paradigm established under Hatch-Waxman of a short exclusivity period followed by patent restoration may not be appropriate. We must recognize this fundamental difference and build a regulatory scheme that accounts for it. If a follow-on manufacturers only has to develop a product that is comparable and not the same it may be easier to engineer around patents. I look forward to hearing from our witnesses on what should be the appropriate incentives for continued innovation.

Again, Mr. Chairman, thank you for holding this hearing. We have a distinguished panel of witnesses. I urge all Members wto take an active, engaged role today because these are complicated issues. This committee has a history of being deliberative busy, we should develop policy based off the facts at hand. This is especially true when we are talking about products that are so important to the well being of millions of Americans.

Mr. PALLONE. Thank you. I recognize the gentlewoman from Wisconsin.

OPENING STATEMENT OF HON. TAMMY BALDWIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WISCONSIN

Ms. BALDWIN. Thank you, Mr. Chairman, and thank you to the witnesses for joining us today. I am really pleased that this subcommittee is taking up the issue of creating a pathway at the FDA for approval of biosimilars, and as many have noted this is a complicated issue full of highly technical, scientific terms and procedures. The fact that we have so many ways to refer to this issue, biosimilars, biogenerics, generic biologics, follow-on biologics, illustrates just how complicated the issue is and how it clearly warrants thoughtful and thorough discussion. So I appreciate the opportunity to delve into some of the details.

Mr. Chairman, I believe that we should have an established process by which the FDA can approve biosimilar products. Biologics have shown great promise in fighting a variety of diseases and conditions, and I believe that we must ensure that patients have access to affordable treatment. That said, I think we also need to remember those patients who are still waiting for their miracle treatment to be discovered. I do not think that we should compromise future innovation so that we can save a finite amount of money today. There is a balance that can and actually must be struck between mere term cost savings and future innovation. I was proud to join my colleagues, Mr. Inslee and Mr. Green, in introducing a bill that seeks to strike this balance. The bill establishes a pathway, ensures that patient safety protections are in place, yet gives the FDA flexibility in this area and provides incentives for scientists to continue innovating and developing potentially lifesaving treatments.

Mr. Chairman, I think one final thing for us to remember is that the majority of biotechnology companies are not mega-corporations or even profitable businesses. The majority of biotech companies are small, private startups who are years away sometimes from even having a commercial product. They are made up of a few highly talented scientists who have made a discovery and who want to continue to explore and refine this discovery in hopes of one day curing cancer or finding a treatment for Alzheimer's or growing new skin for burn victims or responding to a host of genetic disorders for which there is no treatment or cure or creating a better treatment for a disease that already has a treatment, like diabetes. We should encourage this innovation so that future patients can have access to needed treatments just as we should ensure that current patients have access to affordable treatments today.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. I recognize the gentlewoman from Oregon.

OPENING STATEMENT OF HON. DARLENE HOOLEY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Ms. HOOLEY. Thank you, Mr. Chairman. The Drug Price Competition and Patent Term Restoration Act of 1984, better known as the Hatch-Waxman, was instrumental in expanding access to pharmaceuticals by instituting competition and thus lowering prices. I

believe it is important for Congress to examine the creation of a pathway to allow the Food and Drug Administration to approve follow-on biologics. Creating a pathway for follow-on biologics are generally much more complex than the small-moleculed generic drugs that have been approved under the process established by Hatch-Waxman.

First and foremost, as we discuss the creation of a follow-on biologics pathway, safety must obviously be our No. 1 concern.

Second, Congress must ensure science and scientists guide the approval process. Hatch-Waxman struck an appropriate balance between expanding access to affordable generic medications while still encouraging innovation. Biologics have provided some extraordinary pharmaceutical breakthroughs that have made a real difference in the lives of people. However, in part because of that complexity and the very high cost of bringing biologics to market, they are often extraordinarily expensive. It is not uncommon to see treatment cost in the thousands and sometimes tens of thousands of dollars a year per patients in some biologics. The savings that a follow-on biologic pathway may provide to consumers and the increased access that would result would be an important step forward. However, it is also imperative that innovators be allowed to recoup their investment. If we do not include reasonable protection for innovators, we may discourage the development of new products in the future; and that would be even worse for consumers in the current situation.

America is a leader in pharmaceutical innovation, and I am committed to ensuring that we continue that legacy. I look forward to a discussion of intellectual property and patent law issues raised by biosimilars, and I look forward to our witnesses.

Thank you.

Mr. PALLONE. The gentleman from Oklahoma.

Mr. SULLIVAN. I waive my opening statement.

Mr. PALLONE. Ms. Eshoo.

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

Ms. ESHOO. Mr. Chairman, thank you for having this hearing. I am going to place my printed statement in the record. I just want to say a couple of things and that is in this hearing that you have called, which is a very important one, Assessing the Impact of a Safe and Equitable Biosimilar Policy, I think the two words that are really the operative words are safe and equitable. And we are going to explore that today. I am troubled by different parts of Mr. Waxman's bill. He has always been thoughtful when it comes to issues relating to the FDA. The quarrel here is not pathway. Everybody is for a pathway. I think everyone that has spoken has used that word in their opening statement. We agree on that. Do we all want lifesaving drugs and processes to continue to help save people's lives and improve their lives? Everybody wants that. So there isn't any disagreement about that. How this is done is really the rub of the whole debate, and that is what we have to explore. I have really never seen in legislation that has come before this Health Subcommittee, since I have been on it since 1994, when a

legislation actually defined structural characteristics. I mean, I thought that was the job of the FDA.

So I am looking forward to this debate. I think we need to have bipartisan legislation in this area. Why? Because that is what the American people will ultimately have confidence in. We have to build that consensus. So I look forward to it. I am eager to hear from the witnesses and question them and thank you for having this very important hearing.

[The prepared statement of Ms. Eshoo follows:]

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

Thank you Mr. Chairman for holding what I expect will be an enlightening hearing about a very important issue.

The greatest advances in medicine in recent decades has been the development of powerful treatments and therapies for disease that not only treat their symptoms, but also attack them at the molecular level. This is made possible by biotechnology.

We've mapped our own genome and are developing an understanding of how deadly diseases like cancer, diabetes, HIV, and heart disease actually attack the body and its organs.

Biotech researchers are able to analyze the mechanisms of a disease, understand how it functions, and create countermeasures that can cause the disease to stop reproducing, attack itself, or starve it for nutrients. Other biologics help the human body develop an effective response or, in some cases, repress an overactive immune response.

This research is cutting edge, it's risky, and it's expensive. The biotech industry spends billions on research into new biologic treatments, but only a few hundred new biologics are currently in clinical trial, and only a handful of "blockbuster" treatments have emerged.

An example is Genentech, which is considered a founder of the biotech industry over 30 years ago, and remains one of the largest companies in the industry. Today it has only 14 products on the market. The vast majority of biotech firms have only a single product approved or a small handful in development, and it costs upwards of a billion dollars to bring a single biologic to market.

I think it's imperative to consider this framework as we evaluate any proposal to allow "copycat" versions of these life-saving products to take advantage of the research and investment made in biotech.

A lot of the discussion in the debate over follow-on biologics has focused on increasing "access" to life-saving medicine. Certainly the high cost of biologics can stress patients and families, insurance companies and health care providers. We should look at ways to make biologic products more cost-effective. However, simply making copies of products already on the market will not increase the number of biologic products options available to patients. There will be nothing to copy if we don;t ensure sufficient incentives exist to develop these already life-saving medicines in the first place.

Finally, we can't lose sight of what I believe is our most fundamental responsibility, and that of the FDA—protecting the American public.

Whatever else we do, patient safety has to remain our foremost objective and we shouldn't limit the FDA's authority to establish mechanisms to ensure the safety and efficacy of any medicines introduced in the market.

I agree with those who have said that a pathway for new versions of biologic products whose patents have expired is necessary. We also should rely on sound science and develop a system that preserves incentives for the development of new therapies and cures, protects patients, and allows for competition.

I look forward to the witnesses' testimony and their responses to our questions.

Mr. PALLONE. Thank you. The gentlewoman from Illinois, Ms. Schakowsky.

OPENING STATEMENT OF HON. JAN SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. Thank you, Mr. Speaker. Let met take a second to express my thanks for your leadership in bringing this extremely important legislation before our subcommittee.

Biopharmaceuticals are growing at an astonishing rate in the United States, almost twice that of traditional medicines. So as our country, this Congress, and this committee take on the challenge of finding cost savings in our healthcare system, this certainly seems like a good place to start. While opinions vary about the level of the savings patients and the Federal Government could gain from a pathway for generic biologics, no one seems to dispute that the potential for savings exists; and I think it is important to recognize that this discussion is taking place at the State level, too. In my own State of Illinois, for example, a compilation of approximately 100 biopharmaceuticals cost $33.2 million last year and the number of prescriptions for these drugs rose nearly 30 percent. In 1984, the need to bring affordable prescription drugs to those who need them was recognized with the passage of the Hatch-Waxman Act which now brings generic versions of drugs to consumers at about one-third of the cost. Ensuring that this kind of access to lifesaving medicines is expanded to biologics is a critical goal. I think that above and beyond the potential for cost savings lies an obligation, one that I think no one would dispute, to provide Americans with effective and safe medications in a timely way.

Scott McKibbin, a special advocate for prescription drugs for the State of Illinois, is an expert on issues relating to access to safe prescription drugs. He has prepared testimony for the subcommittee's hearing today. I would ask unanimous consent, Mr. Chairman, to submit his remarks into the record.

Mr. PALLONE. Thank you.

Ms. SCHAKOWSKY. No, I wanted to submit remarks into the record from Scott McKibbin.

Mr. PALLONE. Absolutely. So ordered and I indicated earlier that we would allow members on both sides to submit additional statements.

[The information appears at the conclusion of the hearing.]

Ms. SCHAKOWSKY. Let me just finish. Mr. McKibben's testimony is an account of how State budgets are being stretched to the limit as they struggle to maintain access to often lifesaving biologics.

I look forward to hearing from each of our witnesses today as well as working on the issue in the near future. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentleman from Tennessee, Mr. Gordon.

Mr. GORDON. Thank you, Mr. Chairman. I have a splendid opening statement that I am going to submit for the record. I think it is time to hear from our witnesses, so let me just quickly say that healthcare costs are rising at 7 percent a year, much outpacing economic growth in this country. It is certainly the fastest-growing part of the Federal budget. Probably for most families and businesses, it is probably the fastest-growing part of their budget. So we need to look for savingswhere we can, and I think generic drugs is certainly one area.

However, I am concerned that follow-on biologics at this point cannot be safely put in that same category; but I compliment Mr. Waxman for putting this issue in play, and I agree with Mr. Matheson that after a thorough review of this that we can come up with a good solution here. And so I am anxious to hear from our witnesses. Thank you.

[The prepared statement of Mr. Gordon follows:]

PREPARED STATEMENT OF HON. BART GORDON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Each year, health care consumes a larger portion of the Nation's gross domestic product. Health care spending is growing at 7 percent a year—far outpacing our economic growth.

Clearly, we must find ways to bring down the cost of health care. The broader use of generic drugs will surely help. But, sound science must support the decisions we make to ensure patient safety is protected.

I have serious concerns about the assertion that biologics can be treated the same as chemical pharmaceuticals. Biologics are very different from traditional chemical drugs both in their structural complexity and the way they are manufactured. Any process for review and approval of generic biologics or bio-similars must recognize these differences.

Generic chemical drugs can be examined in a laboratory with a simple test to show that the compound is identical to the brand name drug. Biologics can not be tested in the same way. Currently, there is no simple battery of tests to ensure that a generic biologic is not only comparable to the original biologic but can be safely substituted for the original biologic. We need a process of characterization of the biologics to ensure that the medication is what we believe it should be.

The Food and Drug Administration has told Congress that it could be a decade or more before the science is available to safely approve generic versions of biologic drugs. I hope it will take less than a decade to develop reliable tests for biologic drugs. And, we should look closely at the European model that relies heavily on clinical testing before deployment.

Mr. Chairman, I thank you for holding this hearing and look forward to learning more from the witnesses on these issues.

Mr. PALLONE. Thank you. I think that concludes our opening statements. Any other statements for the record will be accepted at this time.

[The prepared statement of Mr. Towns follows:]

PREPARED STATEMENT OF HON. EDOLPHUS TOWNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Thank you, Mr. Chairman, for holding this important hearing today on what is truly a very complex issue.

Advances in science during the past 25 years have resulted in tremendous breakthroughs in how diseases are treated today. Biotechnology has been at the forefront of these advances and holds the greatest hope for patients who suffer from devastating diseases such as cancer, multiple sclerosis, and diabetes. These biotech treatments, called biologics, are highly complex proteins made from living cells—they are fragile molecules which are thousands of times larger than the simple, small molecule chemical pills that we find in our medicine cabinets. This molecular complexity requires a costly research and development process that results in a high price for healthcare payers.

I thank the chairman of this committee for bringing forth the debate on how to lower these costs and provide greater access to these life-saving drugs for our constituents. I believe that Congress should act this year to establish an abbreviated process for follow-on-biologics, just as we did in 1984 for chemical pills through Hatch-Waxman. However, the science is different and far more advanced than in 1984 and we need to take that into account as we craft a new pathway for follow-ons. While a generic company can take a chemical pill and replicate its structure to make an exact copy, I understand the same may not be true for biologics.

Since follow-on products will be made from different cell lines and produced through different processes than the original innovator products, it seems that there

will inevitably be variability in any attempted copies. Given these differences, the traditional generic drug approval pathway seems inappropriate. It is imperative that the FDA know how any differences between biological products and processes will affect a patient before we allow shortcuts to be taken in the approval process, and I believe that clinical trials are crucial to ensuring patient safety. Dr. Janet Woodcock testified in front of the Oversight and Government Reform Committee last month that it will likely be a matter of 10 years before the science is available to fully classify and compare these drugs. In our rush to save dollars, we must not ignore that there is a great deal that we do not know, and I look forward to learning more from Dr. Woodcock this morning.

The issue of follow-on biologics is a very complex one and it would be irresponsible of this Congress to act in this area without knowing all of the scientific facts. We need to be sure that we understand the science before we rush into legislating. I urge the committee to do just that—take the time and not rush the learning process and not stick a bill onto the first moving vehicle.

To balance the concerns over cost, patient safety, and protection of U.S. innovation, I became a co-sponsor of H.R. 1956, the Patient Protection and Innovative Biologics Medicines Act. This bill was introduced by our colleagues, Representatives Inslee, Baldwin, and Green and takes a balanced approach to the issue. Any legislation we move out of this committee must strike the appropriate balance in getting follow-on biologic medicines approved and on the market, while at the same time providing incentives for innovation so that America retains its lead in the field of biotechnology and the next-generation of life-saving medicines continue to be developed.

We are all aware of the critical problem of rising health costs, and the havoc it is wreaking on budgets. There is probably nothing more welcome in these halls than a chance to save taxpayers money on healthcare. Visions of dollars saved are a powerful motivator. My concern is that we don't stampede common sense in the rush to save money. Let's not, for example, create a bill that eliminates rewards for creating the latest, most ground-breaking medicines. Let's be sure to include clear safety requirements that are appropriate for the level of complexity of the different drugs. Let's allow doctors, not insurers, to decide which of these drugs are appropriate for patients. This is a new scientific arena that Congress is entering. Dr. Jane Woodcock testified in front of the Government Oversight Committee last month that it will likely be a matter of 10 years before the science is available to fully classify and compare these drugs. In our rush to save dollars, we must not ignore that there is a great deal that we do not know. In situations where we don't know, I feel we must err on the side of protecting patients from undue harm, and protecting their futures by not squelching the pipeline for new treatments.

Any legislation we move out of this committee must strike the appropriate balance in getting follow-on biologic medicines approved and on the market, while at the same time providing incentives for innovation so that America retains its lead in the field of biotechnology and the next-generation of life-saving medicines continue to be developed.

Thank you Mr. Chairman, for holding this hearing today so that we all may learn more about this issue. I yield back.

Mr. PALLONE. I did want to mention without objection that Mr. Inslee will be joining us. He is not on this subcommittee but is on the full committee, so he will be joining us for questions of the witnesses.

So let me move onto our first panel which just consists of one witness. Dr. Woodcock, if you want to come forward? Welcome. Dr. Janet Woodcock is Deputy Commissioner and Chief Medical Officer for the Food and Drug Administration. You have 5 minutes for an opening statement which becomes part of the hearing record, and you may in the discretion of the committee, submit additional brief statements in writing for inclusion in the record. Right now I recognize you for 5 minutes. Thank you for joining us.

STATEMENT OF JANET WOODCOCK, M.D., DEPUTY COMMISSIONER AND CHIEF MEDICAL OFFICER, FOOD AND DRUG ADMINISTRATION

Dr. WOODCOCK. Mr. Chairman and members of the subcommittee, thank you for the opportunity to testify about the scientific and regulatory framework surrounding follow-on biologics. In considering the complex scientific issues at hand, I have not only relied on my experience in leading the Center for Drug Evaluation and Research for over a decade, but also in my 8 years of experience in working for the Center for Biologics Evaluation and Research, or CBER. While in CBER, I served as Acting Deputy Center Director and Director of the Office of Therapeutics in which capacity I oversaw the approval of biotechnology products to treat serious illnesses such as cancer, multiple sclerosis, and cystic fibrosis.

The success of FDA's current generic drug program has spurred interest in considering abbreviated application pathways for more complex molecules. Currently there are over 9,000 approved therapeutically equivalent generic drugs on the market that constitute more than 60 percent of prescriptions written in the United States. FDA's office of generic drugs currently approves generics at the rate of more than one per calendar day. These generics provide affordable medicines for millions of Americans.

The topic for discussion today is variously referred to as follow-on proteins, follow-on biologics, generic biologics, biosimilars, and so forth. Many of these terms are very imprecise and confusing. Largely what the interest is is in copies of biotechnology-produced protein products that FDA calls follow-on proteins. In the U.S., proteins are regulated either as drugs under the Food, Drug, and Cosmetic Act or as biological products under the Public Health Service Act. Whether regulated as drugs or biological products, proteins fit into the category of complex molecules that can be difficult to fully characterize. Copies of protein products that are regulated as drugs may be considered for abbreviated application pathways that exist under section 505 of that Act. For the very simplest peptide products, manufacturers may be able to demonstrate that they contain the same active ingredient as the innovator product and thus may be considered under 505(j) which is what is commonly regarded as the generic drug pathway.

In contrast, copies of approved protein products that are regulated as drugs would currently be considered for abbreviated applications under 505(b)(2), as scientific techniques are not available to demonstrate sameness of these types of molecules.

Now, as already hasbeen said, an abbreviated pathway, though, does not exist for copies of protein products that are approved under the Public Health Service Act. FDA has approved several follow-on proteins under 505(b)(2) including a recombinant, hyaluronidase and a recombinant version of human growth hormone.

We are currently preparing a guidance document on the general scientific framework for preparing abbreviated applications for follow-on proteins under 505(b)(2), and we expect to follow this with guidance on technical issues such as immunogenicity and physical characterization methods.

FDA is frequently asked how difficult or feasible it is to approve a copy of an existing protein using an abbreviated pathway such

as 505(b)(2). Simple proteins that can be extensively characterized by analytical and functional tests can often be shown to be very similar to an approved protein, and thus the manufacturer might not have to perform extensive clinical testing. However, the clinical tests needed, even for simple proteins, would still be more than what is ordinarily done for a small-molecule generic drug. In contrast, very complex proteins, especially those that are difficult to characterize functionally are more challenging. Using today's science, it would not be possible by using analytical and functional tests alone to be sure that a complex follow-on product was very similar to an innovator product. Therefore, more extensive clinical testing would probably be needed. However, this clinical testing might still fall short of what would be needed for stand-alone new drug application.

Protein products vary in their physical complexity and how well their mechanism of action is understood and the relevance of functional tests as adequate surrogates for their effects, the complexity of their clinical indications, and many other factors. These all must be taken into account in determining how much additional data would be needed to be submitted in an application for a follow-on protein under 505(b)(2). These determinations require a significant amount of scientific and medical expertise. However, FDA is well-prepared to undertake these evaluations given our over 20-year history of regulating recombinant products.

I will be very pleased to answer your questions.

[The prepared statement of Dr. Woodcock follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

STATEMENT OF
JANET WOODCOCK, M.D.
DEPUTY COMMISSIONER, CHIEF MEDICAL OFFICER
FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

"Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States"

May 2, 2007

Release Only Upon Delivery

Introduction

Mr. Chairman and Members of the Subcommittee, I am Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer at the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to testify about the scientific and regulatory background surrounding follow-on protein products.

During the past several years, there has been increasing public interest in the development of follow-on versions of approved protein products. This interest has been fostered, in part, by advances in manufacturing technology, process control, and characterization that allow greater control over, and understanding about, the physical structure of certain of these products.

However, a number of important issues related to development of such follow-on products also have been identified. First, there is general recognition that the idea of *sameness*, as the term is used in the generic drug approval process under the Federal Food, Drug, and Cosmetic (FD&C) Act and applied to small molecules, will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products under the Public Health Service (PHS) Act. Additionally, as a related matter, there are clearly scientific challenges involved in determining that a molecule that is not the same as an approved or licensed version is nevertheless similar enough that the Agency's conclusions about the safety and effectiveness of the approved or licensed version could be relied on to support approval of the follow-on product.

Presently, the PHS Act does not contain an abbreviated approval pathway analogous to the FD&C Act section 505(b)(2) and 505(j) (21 U.S.C. 355 (b)(2) and 355 (j)), although the Agency has approved a number of protein products, such as human growth hormone, under the FD&C Act.

The Administration supports the goal of making safe and effective drugs more available to American consumers. Working with Congress, the Administration has successfully taken steps to speed quality generic drugs to market. We look forward to working with Congress in a bipartisan fashion to consider issues related to a possible pathway for follow-on protein products. Such legislation should, as its first priority, protect patient safety. It should also maintain the research enterprise that has generated valuable, life-saving medications. These complex issues should be considered thoroughly through a robust scientific, regulatory and legal discussion. Such discussion should not be abbreviated for any reason.

Background

Before I go any further, I would like to define some terms and describe the scope of my remarks, so that we can have a common understanding of the issues. I will define additional terms as needed in this testimony as I first outline the pertinent regulatory schema and then describe the scientific issues. First, I would like to recognize that the terms *biologics, generic biologics*, *biogenerics*, and *follow-on biologics* are often used informally to refer to certain products produced through biotechnology. These terms are imprecise and can be confusing, and the use of the term *generic* inaccurately implies the same meaning as exists for generic drugs.

For purposes of this discussion, I will use the term *protein products* to refer to certain biological products licensed under the PHS Act and to certain protein and peptide products approved under the FD&C Act. I will further use FDA's informal term *follow-on protein products* to refer to proteins and peptides that are intended to be sufficiently similar to an approved product to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on protein products may be produced through biotechnology or derived from natural sources.

A *biological product* is defined, in relevant part, under the PHS Act as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment or cure of a disease or condition of human beings." (PHS Act §351(i), 42 U.S.C §262(i)). Many categories of biological products are defined by their clinical use, for example, vaccines and allergenic products. Vaccines can include live attenuated viruses and inactivated viruses, products made from bacteria or other micro-organisms, products made from cells (human or other), and protein products made using biotechnology. Other biological products are defined by their origin (e.g., blood and blood products). Blood products may be made from human blood collections, from blood from animal species, or using biotechnology. Monoclonal antibodies are biotechnology-derived versions of certain blood proteins. Newer types of biological products include cellular therapies (beyond the traditional blood cells) and gene therapies. Many biological products are not completely characterizable using current technology.

Traditionally, some natural source proteins have been regulated as drugs under the FD&C Act, including insulin, hyaluronidase, menotropins, and human growth hormones, while other natural source proteins, such as blood factors, are regulated as biological products under the PHS Act. In the late 1970s and early 1980s, recombinant proteins and monoclonal antibodies began to be developed. Certain of these products were regulated by FDA's Center for Drug Evaluation and Research (CDER) under the FD&C Act as drugs (e.g., hormones such as insulin and human growth hormone), and others were regulated by the Center for Biologics Evaluation and Research (CBER) under the PHS Act (e.g., cytokines, proteins that are involved in the immune response, and blood factors, such as factor VIII for the treatment of hemophilia). In 2003, certain therapeutic proteins regulated by CBER were transferred to CDER, with no change to the applicable regulatory authority. Currently, some proteins are licensed under the PHS Act, and some are approved under the FD&C Act.

At this point, it may also be helpful to set out certain terms that describe how certain products relate to each other.

> *Comparability*
> The current FDA use of the term "comparability" generally refers to the comparison of a biological product before and after a manufacturing change by the manufacturer. A sponsor may be able to demonstrate that a product made after a manufacturing change is comparable to a product made before implementation of the change. This may be demonstrated through different types of analytical and functional testing and might not require additional clinical studies. The Agency may determine that the two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency. (It is important to note, however, that this has generally been applied in cases where the manufacturer and Agency have full access to the manufacturer's data – something that may not be the case for follow-on products.) See April 1996 FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products.

The International Conference on Harmonization (ICH) guidance defines comparable as a conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. See June 2005 ICH Guidance for Industry Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

Therapeutic Equivalents
These are approved drug products, usually made by different manufacturers, that are pharmaceutical equivalents and for which bioequivalence has been demonstrated. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Therapeutically equivalent prescription drugs will receive an "A" equivalence evaluation code in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book). This term has been applied only in the context of drugs approved under section 505 of the FD&C Act.

Interchangeability
This term is not defined by FDA and could have a number of different meanings. It could refer to products that are therapeutic equivalents, and thus could, in some circumstances, be substituted at the pharmacy level without a physician's intervention. Alternatively, the term could describe similar products that are not "substitutable" but which, under a physician's supervision, could be used to treat the same disease or condition in the same patient.

The concept of a follow-on protein product is that an applicant could obtain approval for such a product through the submission of an abbreviated application. An *abbreviated application* would be one that relies, to at least some extent, on the Agency's conclusions regarding the safety and effectiveness (or safety, purity, and potency) of an approved product and also contains whatever additional data is necessary, to establish that the follow-on product is safe and effective. It is important to ensure that facilitating the development of follow-on products through abbreviated pathways does not discourage innovation and the development of new biological products.

Follow-on Protein Products

Generally speaking, the interest in development of follow-on protein products pertains to versions of follow-on products manufactured using biotechnology. As noted, these protein products are either approved as drugs under the FD&C Act or licensed as biological products under the PHS Act. Unlike small molecule drugs whose chemical composition can easily be determined to be the *same* as an approved product, the very nature of protein products makes comparisons of one protein to another, including comparisons to establish safety and efficacy, more scientifically challenging.

Statutory Framework for Drug Approval

FDA approves new drugs, as distinguished from biological products, under approval mechanisms found in section 505 of the FD&C Act and licenses biological products under section 351 of the PHS Act. Under the FD&C Act, in addition to the approval pathway involving the submission of a full 'soup to nuts' new drug application, there are two abbreviated pathways for subsequent versions of already approved drug products.

Abbreviated Approval Pathways Under the FD&C Act

The Abbreviated New Drug Application (ANDA) process in section 505(j) was established through the 1984 Hatch-Waxman Amendments, and reflects Congress' intention to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs and to avoid ethical concerns associated with unnecessary, duplicative human testing. This is an abbreviated approval mechanism for duplicates of drugs already approved under section 505 of the FD&C Act. Under these statutory standards,

a generic drug generally must contain the same active ingredient as an innovator product; it must be bioequivalent to the innovator drug; and it must have the same dosage form, strength, route of administration, labeling, and conditions of use. By establishing that the drug product described in the ANDA is the same as the approved innovator drug product, the ANDA applicant can rely on the Agency's finding of safety and effectiveness for the approved drug. Most drug products approved under section 505(j) are therapeutically equivalent to the referenced approved drug.[1] Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. In many jurisdictions, therapeutically equivalent drugs may be substituted at the pharmacy level, without a physician's intervention. For reasons that I will discuss, it is not clear that this type of pathway, which determines that a drug is the same based on a chemical comparison to the innovator product, would be appropriate for follow-on protein products.

The abbreviated pathway described in section 505(b)(2) of the FD&C Act permits an applicant to rely on published literature or on the Agency's finding of safety and effectiveness for a referenced approved drug product to support approval of a proposed product. The 505(b)(2) applicant must demonstrate that reliance on the previous finding of safety and effectiveness is scientifically justified and must submit whatever additional non-clinical and clinical data are necessary to establish that the proposed product is safe and effective. FDA

[1] Drug products approved pursuant to a petition submitted under section 505(j)(2)(C), which can differ in among other things, route of administration, dosage form, or strength of the drug would not be therapeutically equivalent to the referenced approved product.

has used this pathway to approve some follow-on protein products including human growth hormone.

Scientific Issues

Compared to many small molecule drug products, proteins are usually substantially larger, more complex molecules that may be mixtures of distinct entities. Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variations in the manufacturing process. The quality and nature of natural source products can vary depending on condition of the source material, processes used to extract and purify the product, and other factors.

Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Therefore, the section 505(j) generic drug approval pathway, which is predicated on a finding of the same active ingredient, will not ordinarily be available for protein products.

However, FDA has considerable experience with reviewing some protein products, including cases where the Agency has considered the extent to which existing conclusions about the safety and effectiveness of a protein product could be applicable to another protein product based on data and information showing the similarity of the products. One example, most applicable to this discussion, is the situation in which a different manufacturer has sought to

demonstrate that its protein product is similar enough to a protein product marketed by another manufacturer that the finding of safety and/or effectiveness made for the approved product could be relied on to support approval of the proposed product (e.g., a 505(b)(2) application).

FDA has also considered these issues when manufacturers seek to demonstrate that a new version of their licensed biological product manufactured using a different manufacturing process is comparable to the product manufactured using the original process. However, it should be clear that demonstrating the similarity of a follow-on protein product to a reference product will typically be more complex, and thus require more new data, than assessing the similarity of products before and after manufacturing changes made by the approved product's sponsor.

In general, the amount and type of new data that will be needed to demonstrate the safety and effectiveness of a follow-on protein product, compared to the data that supported the safety and effectiveness of an already marketed product, will be influenced by the extent to which the follow-on product can be demonstrated to be sufficiently similar (structurally, functionally, and clinically) to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product. In addition, the amount and type of new data needed will be influenced by the clinical use of the product and the amount and type of clinical experience that has been accumulated about the approved product as well as related products.

Current technologies, such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein. Conclusive analysis of other aspects of a protein's structure requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself. Such complexities include: folding of the protein's amino acid chain into highly organized structures, post-translational modification of the protein with a broad range of biochemical additions (e.g., glycosylation, acetylation, phosphorylation, etc.), and association of multiple protein molecules into aggregates. It is the combination of the protein's amino acid sequence and its structural modifications that give a protein its unique functional characteristics. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product. Although this currently may be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.

Functional characterization, using *in-vitro* tests, is also of great importance in assessing the similarity of two proteins. For proteins with a well-understood mechanism of action and available functional assays, extensive functional comparisons will enhance understanding of comparability. Future scientific advances may facilitate the ability to perform more meaningful functional testing.

Protein products are used for a wide variety of indications. In some cases, there is an extensive mechanistic understanding of the role of the product in the treatment process. For example, some products are used as replacement therapies to treat a known deficiency (e.g., human growth hormone for growth hormone deficiency). For some such products, the mechanism of action and the role of replacement are well understood. In the case of other products, the mechanism of action of the product is not well understood and its role in treatment was derived, in part, by trial and error. In such cases, even very extensive structural and functional comparisons between a follow-on and a comparable innovator product may not be sufficient to allow broad reliance on conclusions regarding a prior product. When the mechanism of action is well understood and there is a significant amount of clinical experience with a product, it may be easier to make a scientific assessment of the ability to rely on conclusions about safety and efficacy from a prior application.

Immunogenicity is the ability to stimulate an immune response. An immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies, to an immune response with impact on safety or effectiveness. "Neutralizing antibody" responses can decrease the clinical effect of a protein. Adverse safety events from an immune response could include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous (naturally occurring in the body) protein (e.g., erythropoietin). Immunogenicity may be influenced by patient-related, disease-related, or product-related factors. Immune responses to administered protein products can be extremely serious or life-threatening; therefore, this issue requires significant attention.

The ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited. Therefore, some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed. The extent of independent testing needed will again depend on a variety of scientific factors such as the indication, whether the product is to be administered chronically, the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule.

A finding by the Agency that a follow-on protein product may be approved as safe and effective is distinct from a determination that the follow-on protein product would be substitutable for the referenced protein product. To establish that two protein products would be substitutable, the sponsor of a follow-on product would need to demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity. For many follow-on protein products -- and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.

Examples of Approvals

Even though protein products are more complex than small molecules, FDA has applied its expertise and experience to approve certain follow-on protein products in applications

described in section 505(b)(2) of the FD&C Act. Some examples of products approved in this manner are: Hylenex (hyaluronidase recombinant human), Hydase (hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatropin [rDNA origin]). I will discuss, in detail, two of these examples of protein products that were approved through an abbreviated approval pathway.

Omnitrope (somatropin)

Omnitrope is a human growth hormone product derived from recombinant DNA processes. Human growth hormone is a single-chain, 191 amino acid, nonglycosylated protein. Its amino acid sequence is well known and physicochemical tests are able to determine the complex folded structure of human growth hormone products. There are also clinically relevant bioassays and validated biomarkers (laboratory indicators of effect) available to assess the performance of human growth hormone products.

Human growth hormone has a long and well-documented clinical history as replacement therapy for growth failure in pediatric patients due to endogenous growth hormone deficiency, and its mechanism of action and toxicity profile are well established. Some marketed human growth hormone products are approved for other uses, such as therapy for growth failure associated with chronic renal insufficiency and replacement of endogenous growth hormone in adults with growth hormone deficiency.

The original marketed versions of human growth hormone were derived from the pituitary glands of human cadavers. The first recombinant version was approved in 1985. Since then,

several more recombinant human growth hormone products have been approved under section 505(b)(1) of the FD&C Act (i.e., each product approval relied on original clinical data developed specifically for that product, not an abbreviated pathway).

Omnitrope is the first recombinant human growth hormone product approved through the abbreviated pathway described by section 505(b)(2) of the FD&C Act. It was approved for (1) long-term treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone and (2) long-term replacement therapy in adults with growth hormone deficiency (either childhood or adult onset). The approval of Omnitrope was based on new data specific to Omnitrope (but less new data than would be needed to support an approval under section 505(b)(1)) and also relied on the approval of Genotropin (a previously approved version of rDNA-derived somatropin) for the same indications proposed. Specifically, the approval was based on the following:

- Physicochemical testing that established, among other things, that the structure of the active ingredient in Omnitrope is highly similar to the structure of the active ingredient in Genotropin;
- New non-clinical pharmacology and toxicology data specific to Omnitrope;
- Vast clinical experience and a wealth of published literature concerning the clinical effects (safety and effectiveness) of human growth hormone;
- Pharmacokinetic, pharmacodynamic, and comparative bioavailability data that established, among other things, that Omnitrope and Genotropin are highly similar based on pharmacokinetic parameters and pharmacodynamic responses;

- Clinical efficacy and safety data from controlled trials comparing Omnitrope to Genotropin and from long-term trials with Omnitrope in pediatric patients; and
- FDA's conclusions that Genotropin is safe and effective for the indications for which approval was sought in the Omnitrope application and that Omnitrope is highly similar to Genotropin.

Omnitrope has not been rated by FDA as therapeutically equivalent (that is, substitutable) to any other approved human growth hormone product.

Hyaluronidase

The hyaluronidases are enzymes that break down hyaluronic acid and chondroitin. Hyaluronidase injection is indicated for use to increase the absorption and dispersion of other injected drugs and for related uses. The enzymatic activity of this product is one of its critical quality attributes, and a method for assessing the enzymatic activity of hyaluronidase is described in the U.S. Pharmacopeia (USP). Most hyaluronidase products are natural source proteins, purified from mammalian testicles, whose amino acid sequences vary based on the species and the tissue from which it is obtained. There may also be variability within the same tissue source.

The first hyaluronidase product was approved for marketing in 1948 under the FD&C Act, based on a literature review demonstrating its safety. Hyaluronidase products containing mammalian hyaluronidase enzyme preparations were subsequently determined to be effective for their current indications. In addition, an extensive body of literature has been developed

supporting the safe and effective use of mammalian testicular hyaluronidase for these indications. FDA has approved follow-on versions of mammalian testicular hyaluronidase (ovine and bovine) under section 505(b)(2) of the FD&C Act (i.e., via an abbreviated pathway) for the existing indications and has more recently approved a human recombinant hyaluronidase follow-on product. For new follow-on hyaluronidase products, the potential for allergic reactions is the primary clinical safety concern. Therefore, in addition to requiring that a given product have the necessary enzymatic activity, the Agency now requires clinical data to assess the allergenic potential of that product. In addition, an applicant is required to provide assurance that its standards for manufacturing ensure consistency of the drug substance and drug product. No hyaluronidase product is rated by FDA as therapeutically equivalent (that is, substitutable) to any other approved hyaluronidase product.

FDA Activity Related to Follow-on Protein Products

Because there are many challenging scientific and policy questions about follow-on protein products, FDA has actively promoted a public dialogue on these issues. FDA has held two public meetings (September 2004 and February 2005) and co-sponsored a workshop, in collaboration with the National Institute for Standards and Technology, and with the New York Academy of Sciences (December 2005), to gather input on scientific and technical issues related to follow-on protein products. These meetings resulted in a large number of comments and concerns from the interested parties that have informed our considerations of these issues.

My fellow FDA scientists and I recently published an article in *Nature Reviews Drug Discovery*, illustrating FDA's scientific reasoning and experience with the approval of certain protein products. This journal article outlines past examples of FDA's actions involving the evaluation of various types of follow-on and second generation protein products and within-product manufacturing changes.

The Agency previously indicated its intention to issue guidance documents to specifically address human growth hormone and insulin. But, as our knowledge of this issue expanded, we reconsidered our focus and determined it would be more appropriate to initially promulgate guidance that is more broadly applicable to follow-on protein products in general. We are in the process of developing such guidance, which would first be released in draft form for public notice and comment, with respect to products approved under the FD&C Act. Of course, as you know, even in the absence of published guidance, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product for submission in an application under section 505 of the FD&C Act. Thus, the Agency continues to review and approve certain follow-on protein products under its current authority and works to do this as effectively and efficiently as possible. Although we currently work closely with all product sponsors to assist them through the FDA review process, as discussed earlier, the Agency plans to address scientific considerations related to the approval of follow-on protein products in a comprehensive manner through issuance of a series of guidance documents. We expect this approach will provide useful guidance to industry while ensuring that we not stifle innovation or the use of state-of-the-art

technologies. We appreciate the interest that Congress has always demonstrated in working to provide safe, effective, and affordable medicines to consumers.

Conclusion

I appreciate the opportunity to provide this background information on the important issue of follow-on protein products.

Mr. PALLONE. Thank you, Dr. Woodcock. I am going to recognize myself for 5 minutes for questions, and then we will go around the committee; and each member will have some questions.

Many people have focused on your previous testimony before the Oversight and Government Reform Committee which you reiterated in your written testimony today. Specifically you state, and I quote, that

> the amount and type of new data that will be needed to demonstrate the safety and effectiveness of a follow-on protein product will be influenced by the extent to which the follow-on protein product can be demonstrated to be sufficiently similar to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product.

Now, you went on to discuss the clinical trial should not be conducted simply for checking a box as part of the regulatory procedure for FDA approval, and I am hoping that you can expand on these statements today. But specifically, can you tell me whether or not you think clinical trials should be required or mandatory for every follow-on protein as you used the term and that applies for FDA approval or do you think that it makes more sense to allow the FDA to have the authority to determine what types of studies or level of science is required to determine approval which is basically what Mr. Waxman has proposed in his legislation.

Dr. WOODCOCK. With the science we have today, we are not able to determine everything about a protein product based on tests in the test tube so to speak, in the laboratory, and in animals. And we would foresee right now, with the science we have today for protein products, we would be looking at additional clinical trials. Depending on the situation, those might be very limited. They might really have to do with the safety issue called immunogenicity, the ability or the propensity of the protein to cause an immune response in people. That is something we really have great difficulty predicting just from laboratory tests, and it is influenced to a great extent by the kind of contaminants that are in the product which has to do with how the product is produced.

Mr. PALLONE. So you want the flexibility as to whether to have the clinical trials, depending on the circumstance?

Dr. WOODCOCK. I think it needs to be considered that the science will advance over time. As many of the members have alluded to, science is advancing very rapidly. What we can do today is somewhat limited, but analytical and functional technologies are advancing rapidly and we may be able to make more exact comparisons in the future.

Mr. PALLONE. OK. I wanted to ask about the issue of interchangeability. You stated in your testimony today, and I quote,

> from many follow-on protein products, in particular the more complex proteins, there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-up protein products may be limited.

That is your quote.

Now, has the FDA ever approved a follow-on protein product as interchangeable with a reference product and if so, can you characterize these products in your ability to determine interchangeability? In other words, were these products simple or more com-

plex molecules and depending on the level of complexity what levels of studies were used to determine interchangeability?

Dr. WOODCOCK. We have not approved protein products as interchangeable. We have not. We have ideas, as I said. We are considering issuing a guidance on immunogenicity, and that would include this issue of switching. Immunogenicity does not really enter in so much with small molecules. Some small molecules actually do cause an immune response, but under the generic program that we have, they are identical. We know that generic copies are identical to the original copies and would be expected to have the same immune response. However, with proteins, proteins themselves, even one product, an innovator product, will vary slightly from batch to batch because they are very complex. So we don't know if you were taking one and if you were switching to another and you switch back and so forth if this might set up an immune response that wouldn't occur if you had just stayed on the same product all along. And that could be very dangerous in some circumstances.

Mr. PALLONE. OK. And then lastly I wondered if you could comment on whether or not you think it would be appropriate to have open and public procedures for all stakeholders to participate in the development of criteria for the approval of follow-on products, as well as what types of post-markings, surveillance, or studies should be required of follow-on protein products? Should the market for pre-market approval and requirements for post-marketing differ from follow-on protein products than reference or products or should they be the same?

Dr. WOODCOCK. That is a lot of questions.

Mr. PALLONE. I know.

Dr. WOODCOCK. We attempt to always have an open and public process for the scientific and technical standards that are used to approve products, and actually we work internationally with the other international regulatory bodies on standards so that different trials don't have to be repeated in different countries and so forth. So it is very important to have an open and public process. We have had multiple scientific meetings, some with various scientific bodies at the New York Academy of Sciences on various aspects of characterization of proteins and so forth and so on. So yes, it is very important that we have continuing, high-level scientific input and dialogue on all of this, including the clinical parts of it.

Mr. PALLONE. OK. Thank you. Mr. Deal.

Mr. DEAL. Thank you, Dr. Woodcock, for being here today. We are dealing here with two statutes, and you referenced the Food, Drug, and Cosmetic Act, specifically 505(b)(2) as a certain pathway and then of course the section 351 of the Public Health Service Act that I believe you say is where the biologics have generally been registered, is that correct?

Dr. WOODCOCK. That is correct.

Mr. DEAL. Would the pathway for follow-on biologics need to be addressed in both of those statutes?

Dr. WOODCOCK. As I said, we have already approved several follow-on proteins under 505(b)(2). There is a pathway already there. We have approved human growth hormone which is a recombinant product and hyaluronidase which is actually a very complicated protein. So that pathway is currently available. However, the pro-

tein products approved under 505 are typically only the hormones and the enzyme products. Most of the others are under the Public Health Service Act which does not have a pathway.

Mr. DEAL. So specifically as to the Public Health Service Act, there would need to be a pathway of some sort. One of the issues that we have all been concerned about is the safety and effectiveness of a follow-on or any product, and I believe you said FDA has the capacity to make those determinations. Am I correct that the current law does not mandate the way that you determine that in terms of mandating clinical trials, that that is simply something you have done under the auspices of legislation, that you have set out those kind of protocols?

Dr. WOODCOCK. Under the Public Health Service Act?

Mr. DEAL. Yes.

Dr. WOODCOCK. The Public Health Service Act requires that the products be pure, potent, and so forth and safe. It does not require specifically clinical trials or any given——

Mr. DEAL. But you have the ability to do those trials because you are charged with the safety and efficacy issue?

Dr. WOODCOCK. Right, and obviously the products have to be safe and effective.

Mr. DEAL. Right. I want to get into a little bit of a detailed discussion about an area that I still don't fully understand. We have had private conversations and in trying to make an analogy to the current generic drugs, the discussion dealt with what FDA can do with the data from the licensed or patented product. And there was a distinction that you made between having access to the data and being able to rely on the data for follow-ons or for generics.

As I understand it Hatch-Waxman allows you to rely on the data for abbreviated new drug applications, is that correct?

Dr. WOODCOCK. That is correct.

Mr. DEAL. OK. Would you elaborate on what you need in this area of follow-on biologics as it relates to this already-accumulated data? What are your restrictions and what do you foresee as reasonable expansions of your current right to either rely on or have access to the data?

Dr. WOODCOCK. To explain this to the members who may not be—this is pretty arcane, I think. Our legal interpretation of the current statute that we rely on says that we rely on the fact of the approval of the innovator product. We are not going in and comparing the data that is in the application of the innovator product to the data that is submitted by the generic manufacturer, all right? So we are relying on the fact that it was approved, safe, and effective and we can bridge back to that approval by the fact that the generic small molecule is the same small molecule and it also is the same dosage for them and so forth and it is bio-equivalent, all right? So then we say if you meet those criteria, then the fact that we approved that product pertains to the generic product.

With follow-ons, it is a little more complicated for the 505(b)(2) world. We are also still relying upon the fact of the approval of an innovator product, but the follow-on protein may not be an exact copy. But again, we are not going in and looking at the data in the innovator application and applying it to the follow-on.

For future products that we would look at, this of course, is somewhat limiting to the FDA in the fact that we can't make direct comparisons of perhaps the pharmacokinetics of one product to the pharmacokinetics of the follow-on product unless that is in the literature somehow or somehow otherwise available. So the extent to which we can approve complicated follow-on products is somewhat governed by the ability to which we can refer to and look at data about an innovator product. We cannot do that now.

Mr. DEAL. Thank you. My time has expired.

Mr. PALLONE. Thank you. Mr. Waxman?.

Mr. WAXMAN. Thank you, Mr. Chairman. Dr. Woodcock, as I understand what you are saying is that it is a lot easier to approve the generics under the Hatch-Waxman Act because you are showing that it's the same drug in effect. Now we have something a little bit more complicated, but we shouldn't throw up our hands and say it is impossible because under a quirk in the FDA law now, you are able to approve a follow-on drug for some proteins that would be in that category of these biogeneric drugs, is that correct?

Dr. WOODCOCK. That is correct. We have approved some.

Mr. WAXMAN. You have approved some? So you have some experience. You have said to us that some of these others are going to be more complicated and therefore more difficult because the science hasn't caught up with it. The biotech industry argues in their testimony today that any legislation authorizing approval of follow-on biologics must require substantial pre-clinical testing and clinical studies including comparative clinical trials to determine whether there are significant differences between follow-ons and reference products in terms of safety and effectiveness. Do you believe good science will always into the future require that substantial pre-clinical and clinical studies include comparative clinical studies and effective are going to be required? Is that micromanaging FDA too much?

Dr. WOODCOCK. I believe that there will always be substantial non-clinical, in other words, laboratory and to some extent there will be animal studies in the foreseeable future comparing two products or characterizing the follow-on product. That is just a routine standard for any drug that we get onto the market, as it would have very extensive testing before it would be put on the market.

For 505(b)(2)'s, the extent to which clinical trials would be required depends on all the factors I went over in my oral testimony. There are a great many factors that have to be brought into play, and there is a spectrum of——

Mr. WAXMAN. Well, science is going to evolve. Right now you would probably agree that there ought to be clinical trials for some of the biologic generics, in other cases you might not. I guess the question is would it be mandated that under every circumstance there would be a clinical trial and wouldn't that end up requiring unnecessary and therefore unethical trials in the future if we required it by statute rather than leaving it to FDA's discretion?

Dr. WOODCOCK. Well, as we said in the testimony, requiring trials simply to require trials is not usually considered a fair use or ethical use of human subjects. We should do trials in people if we need information in people. Right now as I said for proteins, we believe we will need immunogenicity trials in people because we

cannot predict the immunogenicity answers without doing human trials.

Mr. WAXMAN. Do you believe it is better to have a statute that freezes the science as of the date of enactment or that gives FDA the flexibility to tailor requirements as science evolves?

Dr. WOODCOCK. Because the science is so dynamic and none of us can predict where the science is going to go over the next decade, it is evolving unbelievably fast, obviously we all need to be humble before that and have a scheme that I think allows the science to operate.

Mr. WAXMAN. You responded to Mr. Pallone that public process is important for establishing standards for drug approval. I understand you to mean general standards applicable to all drugs or biologics, is that correct?

Dr. WOODCOCK. It depends on the question. I think it is very important in this area, follow-ons, that we stay up to date with the science; and therefore, we have a dynamic public process that keeps giving us the scientific input that we need.

Mr. WAXMAN. Well, do you think it appropriate to always have a public process to establish the correct approval standards for each new product before FDA can take any action or would that cause unnecessary delays?

Dr. WOODCOCK. We have not done that. For example, with the hyaluronidase product that we approved and so forth. So it is going to depend on the situation. In some cases, it might be desirable to have a public process because of so many open questions. In other cases, obviously the path will be very clear.

Mr. WAXMAN. Well, I guess it comes down to in my mind these are some tough decisions. Who ought to make them, politicians here in Washington with Congress saying this is how you must decide the science or should we give you the flexibility with the standards and ask you to make sure the product meets those standards? That is what we have done with all other drugs, both the new drugs especially and other generics or simple or only has to be a copy. In this case, it is not just a copy, but the decision has to be made; and I would trust the FDA to make that decision, not Members of Congress spelling it all out.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Waxman. Our ranking member, Mr. Barton.

Mr. BARTON. Thank you, Mr. Chairman. Dr. Woodcock, if currently I am a manufacturer of a biologic drug and I am making it in batches, is each batch identical?

Dr. WOODCOCK. Not to the state that you would use for identical for chemical drug because we can't tell. For most of the complex proteins, they have a range of forms within the product. It isn't just one protein. There are minor variations in most products that are part of the product. Second, the extent of those variations will change a little bit from batch to batch.

Mr. BARTON. When you say a little bit, what percentage terms? Half a percent, a thousandth of a percent?

Dr. WOODCOCK. Maybe half a percent or so.

Mr. BARTON. Now, will each batch have the same efficacy, the same result?

Dr. WOODCOCK. What we do is we control variability to the point that the product, whether it is a drug or a biologic, should have the same clinical effect time after time. That does not mean though that that product is identical time after time. And that is true with any manufacturing process. You have to control variability down to the point where it doesn't make an impact on the customer.

Mr. BARTON. Well, if the patent expires on a biologic and the same manufacturer in the same location using the same equipment and the same process and the same ingredients made the same product after the patent expired, would that be the same as a generic drug for a biologic drug?

Dr. WOODCOCK. The innovators continue often to make their products after the patent expires. They continue to market their products under their brand. That is still considered the innovator drug.

Mr. BARTON. It would not be considered generic-similar drug?

Dr. WOODCOCK. No. Now, sometimes manufacturers take that product and they give it a different name and they market it.

Mr. BARTON. We understand what a generic is for a normal drug. We understand that for biologics, you really can't call it a generic but is it fair to say that it is similar to a generic?

Dr. WOODCOCK. It would be similar to a generic because the doctors and patients could use it and expect to have the same effect as the innovator drug.

Mr. BARTON. Your standard is going to be the same clinical effect, then you are going to label it as a biologic-similar generic, generic-similar?

Dr. WOODCOCK. That would be one scheme, all right? However, we wouldn't label as interchangeable as we already discussed, that one could be switched for the other unless that had been proven that that was safe to do.

Mr. BARTON. We are kind of going around each other here. What I am trying to get at, when the pharmaceutical reps come in to see me and I assume everybody else on this committee, they don't come right out and say, oh, no, we don't want the generic for biologics. They are not fighting that. They are just saying make sure you do the clinical trials, make sure that it has the effect, depending on the standard that the FDA establishes. You could make it almost impossible, you, the FDA, to have an equivalent to a generic drug for biologics. Do you understand what I am saying?

Dr. WOODCOCK. I do. First of all, let me say we have approved several follow-on recombinant proteins under the Food, Drug, and Cosmetic Act already. They have very similar indications to all the other products that they are similar to——

Mr. BARTON. What I am trying to get at, and I am not doing it in a very efficacious fashion, but I want to hear somebody like yourself, the FDA, says it makes good policy sense to set up a scheme to do biologic follow-ons because we think it is possible and we think it would save consumers money if we do it, instead of these are too large and too complex protein molecules and we just don't think it makes sense because they are so dissimilar to regular drugs.

Dr. WOODCOCK. Yes. Well, as I have said, we feel it is possible and we are doing it under the pathway, where we have a legal

pathway. We have done these approvals already, No. 1. Number 2, however difficult it might be now for some proteins, it can be expected in the future as science evolves, we will be able to make these comparisons more readily and we will be able to do this more easily.

Back in 1984 after the first of the generic drug amendments were passed, there was a period where there was great difficulty in establishing the standards and so forth. But as I said, we now have 9,000 generic drugs.

Mr. BARTON. What do we need to do as a Congress and this subcommittee to make it easier to facilitate the review and approval of biologic follow-ons?

Dr. WOODCOCK. There is no pathway under the Public Health Service Act. So although there is a pathway under 505(b)(2) of the Food, Drug, and Cosmetic Act, and we are using that pathway, there is no similar pathway under the Public Health Service Act.

Mr. BARTON. Do you think it is possible legislatively to create such a pathway?

Dr. WOODCOCK. We would look forward to working with the Congress on these discussions.

Mr. BARTON. Thank you, Mr. Chairman. That is the answer I wanted.

Mr. PALLONE. Thank you. Our vice chairman, Mr. Green?

Mr. GREEN. Thank you, Mr. Chairman. Dr. Woodcock, since biologics are derived from living cells and there is always the chance the patient would develop an undesirable immune system response to a follow-on biologic, the safety issues concerned to me and many patients on biologic therapies already have vulnerable immune systems, is it correct to say that we do not currently have laboratory animal models that can correctly and reliably predict unwanted immune responses for humans?

Dr. WOODCOCK. That is correct.

Mr. GREEN. Within the large group of biologic products, I understand we know a great deal about insulin and human growth hormone but considerably less about other newer therapies. However, human insulin and human growth hormones, so-called simple proteins, the following example in Europe has suggested that testing for a negative immunity response is critical. For example, and this is a very long question that I will run out of time just going through it, but Novo Nordisk worked to develop the second generation of insulin, one that would be fast acting to help control mealtime rise in blood glucose for individuals with diabetes. Two of their next generation drug candidates were fully characterized and both included only one different amino acid. During pre-clinical studies in Europe, Novo Nordisk pulled one candidate because of increased tumor potential found in rats. The other candidate, which hadonly one amino acid, NovoLog, which during trials was determined to have a safety level on par with human insulin.

We have a second example of the European system, Omnitrope, a second-generation human growth. Because Europe requires clinical trial data for biosimilar applications, the manufacturer conducted a clinical trial and again, I could go on.

Is there any instance in which you think a clinical trial to determine immune system response is unnecessary?

Dr. WOODCOCK. For very short peptides which are not really proteins. They are very, very short, small protein-like molecules. That would probably be the case. However, at this time, as I said, for proteins we feel we would need a human trial for immunogenicity at the minimum because we cannot predict immunogenicity from the lab and animal tests. However, I also would like to say that a change in even a single amino acid is not a trivial change whatsoever. That is a very big change and it is easily detectible and we would know all about it. That wouldn't be identical to an innovator product because it would be an obvious change. We refer to that as a second-generation product because it has been changed for some reason.

Mr. GREEN. OK. So to answer the question, you think clinical trial, even those for second generation are needed?

Dr. WOODCOCK. Currently for immunogenicity. Clinical trials might also be needed to answer other questions if there are remaining uncertainties. I think it is important to understand that there is a wide range of clinical trials. An immunogenicity trial can be fairly straightforward. You expose people to the product and you see what happens to the immune response.

Mr. GREEN. In response to Chairman Pallone's questions about interchangeability, you touched on dangers that result in patients from switching biologic products. Given your answer to the question, would you have concerns with Congress allowing, for example, a pharmacist to dispense a follow-on product outside a physician's orders?

Dr. WOODCOCK. The system we have right now, the States regulate of course the practice of pharmacy, but FDA provides a rating, an interchangeability rating, for products that we approve. And if they get that rating, that means that FDA thinks they are interchangeable, and often then the States will follow that and allow the switching at the pharmacy level.

Mr. GREEN. OK.

Dr. WOODCOCK. So at this point in time for proteins, none of those have been granted interchangeability.

Mr. GREEN. And I guess our concern, we want to make sure the tests are done particularly on the second generation.

Thank you, Mr. Chairman. I yield back my time.

Mr. PALLONE. Thank you. The gentleman from Michigan, Mr. Rogers.

Mr. ROGERS. Thank you, Mr. Chairman. I am just going to go down just a little bit of a different path if I may here. The CDC and the Department of Agriculture have deemed 44 particularly dangerous pathogens and toxin, they call them select agents, like ricin or anthrax, smallpox, others I mentioned in my opening statement. You are aware that some of these biopharmaceutical companies are using some of these select agents in the development of their product, is that correct?

Dr. WOODCOCK. Yes. Obviously the Government would be aware any time a select agent is being used in manufacturing.

Mr. ROGERS. But that is not something you regulate through the FDA? It is regulated through Agriculture, CDC, if they are going to get access and use these particularly dangerous select agents. Do I understand that correctly?

Dr. WOODCOCK. If for research or experiments that don't involve humans, the FDA may not be involved, similar to what research goes on at universities or companies. Once manufacturing is leading to human trials, then the FDA is involved, including the manufacturing.

Mr. ROGERS. So the manufacturing side but if I am going through the process of developing a product, would you have anything to do with them gaining access?

Dr. WOODCOCK. No, as I said, similar to universities or other sites, this is regulated by the entities you referred to.

Mr. ROGERS. And I only bring this up, I was in Libya recently and was at a factory where they were making, and have subsequently cooperated with the United States and have turned it over, but they were making mustard gas and they were using one of these 44 particularly dangerous agents to try to weaponize this particular agent. So it is pretty dangerous stuff which is why we regulate it, and you would agree that we need to continue to regulate that pretty closely, do you not?

Dr. WOODCOCK. Certainly.

Mr. ROGERS. If we are going to expand this, I am concerned, how do we make sure—we go through a pretty select process now for these companies which following the regulation costs money, right, and adds to this $1.2 billion in their development. How is the FDA going to ensure that we do not allow these select agents from these products widespread use and increase the number of entities acquiring and using select agents?

Dr. WOODCOCK. Well, first of all, let me say that the vast majority of biological products are not made from select agents or have nothing to do with select agents. What you are talking about is some of the vaccines and perhaps certain cancer therapies that may have various toxins linked to them.

Mr. ROGERS. And pain care, as well, is it not? It is my understanding that there are those that who working to—when they are talking about some pain treatments?

Dr. WOODCOCK. That is possible, however——

Mr. ROGERS. Anatoxins, tetrotoxins.

Dr. WOODCOCK. Right. The types of biotech products that are being talked about here today, the vast majority of them do not involve any of that, OK? That is a very small universe that I would think everyone would agree requires very good oversight.

Mr. ROGERS. But it is important that we keep an eye on those, don't you think?

Dr. WOODCOCK. Absolutely.

Mr. ROGERS. And so if we are going to get into this, don't you think that we ought to be very careful about how we look at who has access to these types of select agents? It is very important that these biopharmaceutical companies have access for research on these kind of things. They can have some certainly medicinal effects. I guess the venom from an Australian marine cone snail is even used in some of these developments. We should encourage that but my fear is that we throw open the door. Is this something that the FDA has thought about if we go to this next generational research entities using these dangerous toxins?

Dr. WOODCOCK. Well, let me reiterate, generally the firms doing follow-ons will not be engaged in R&D of that type. They are not going to be engaged in basic research and so forth. They are going to be focused on making copies of these existing products.

Mr. ROGERS. But in order to do that you would have to have these select toxins if that in fact is a component——

Dr. WOODCOCK. If it is a component, yes, and that can exist. It is a very small universe and requires and has very special controls on it.

Mr. ROGERS. It is a small universe now but if we go to generics just by definition, won't it be a larger universe?

Dr. WOODCOCK. Yes, I can't predict where the market—it depends on how attractive the particular agents are for copying.

Mr. ROGERS. In the average time of that 15 years and $1.2 billion, how much of that was FDA or Government money, on the average in the development of a biotech drug? Does the FDA give them money?

Dr. WOODCOCK. No.

Mr. ROGERS. So pretty much all of that money is private-industry generated, and wouldn't you think it is important that when we go through this we should try to find some answer here but shouldn't we protect that private investment of $1.2 billion? There's not enough money in the world for us to come up with that $1.2 billion?

Dr. WOODCOCK. Right. I think that is one of the tasks before Congress.

Mr. ROGERS. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentlewoman from Wisconsin.

Ms. BALDWIN. Thank you, Mr. Chairman. Dr. Woodcock, we have certainly heard from some innovators that because they make manufacturing changes to their products, sometimes without clinical trials, sometimes with, that perhaps the logical next step is that we could allow generic companies to make biosimilars without requiring clinical trials. But I wonder if there is an equivalency here because sometimes the simple manufacturing changes by brand manufacturers, like changing a filter, for example, are these the same as the type of changes that can be anticipated and I think expected of a follow-on biologic company that does not have access to the original cell line or the original manufacturing process? I wish you would speak to that.

Dr. WOODCOCK. There is obviously a great spectrum of changes that could be made to a product, and manufacturers frequently make small changes to their production process. They often have to do extensive testing, but it is usually not to human testing but it might be very extensive laboratory and sometimes, say, animal pharmacokinetic tests. And even sometimes change of filter has resulted in a dramatic change. It is very interesting.

So change of a whole manufacturing site, a new cell line, and so forth is of much greater magnitude and would require even much more extensive testing, whether it was the innovator manufacturer or there was a follow-on. Change to a whole new manufacturer with a whole new process in cell line and so forth is the largest kind of change you can imagine and would require obviously more testing and so forth than any of these other kinds of changes.

So there is a spectrum. FDA has a lot of experience regulating these manufacturing changes within the innovator industry, and we also bring that experience to bear in looking at a much bigger change which is a whole new manufacturer of the product.

Ms. BALDWIN. Just one other question. As you approach this topic and of course, we are delving into it more deeply and learning a lot about a very complex issue, but it seems to me that when you start out regulating something that there is very little experience with, one wants to start erring on the side of caution by going slow and engaging in strong safety studies. And I just would ask very generally, would the safety assessments that you spoke of during your testimony be as strict as those for the original biologic? Is that what you would contemplate at this point?

Dr. WOODCOCK. As I said, there is a spectrum. In some cases, very extensive safety testing in humans may really not be necessary because we know enough about the product from long time clinical experience as you said, for example, insulin. There are many, many varieties of insulin on the market right now. In other cases, we might need extensive clinical safety testing. In some cases we may need human pharmacokinetic studies and pharmacodynamic studies and pardon me if I am getting into too much jargon here, but there is an ever-widening spectrum of clinical testing that could be done depending on how much certainty remains. After you look at all the pre-clinical testing that has been done and you compare the two products and you say how uncertain are we? Well, if we are very, very uncertain still, it is going to require a lot more human testing. If we are pretty certain and we have a lot of confidence, then it will maybe require immunogenicity testing, perhaps not much more.

Ms. BALDWIN. Thank you.

Mr. PALLONE. Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. Dr. Woodcock, thank you for being with us today. I want to read a quotation, something you said last week. I quote, "Unlike small molecule drugs whose chemical composition can easily be determined to be the same as an approved product, the very nature of protein products makes comparison of one protein to another, including to establishing safety and efficacy, more scientifically challenging." I thought that was important and particularly in light of several questions that I have. I have several and I want to get through them as quickly as I can, so I would appreciate your brevity as well.

Do the safety concerns with biologic products dictate the need for pre-market and post-market clinical studies and post-market surveillance for follow-on biologic products as well?

Dr. WOODCOCK. As I have said, there is a spectrum. Ordinarily we would expect some pre-market clinical studies. I think we may well expect some post-market clinical observations at least to confirm what we have found pre-market.

Mr. FERGUSON. Other countries obviously do this already. The U.S. in your opinion would not want to be the first country that leaves the door open to follow-on biologics without clinical trials, is that correct?

Dr. WOODCOCK. We have approved several follow-on biologics already. They have had clinical trials. We regard that most proteins now would require some degree of clinical testing.

Mr. FERGUSON. Should we do it without clinical trials?

Dr. WOODCOCK. We shouldn't do anything that leaves us with too much uncertainty about the results. We need to know that the products would be safe and effective.

Mr. FERGUSON. Do you think a lack of clinical trials leaves uncertainty?

Dr. WOODCOCK. Currently it would because we can't predict immunogenicity.

Mr. FERGUSON. OK. Under what circumstances could the FDA anticipate that no clinical data would be needed to approve a follow-on? Is there any circumstance that you can think of currently?

Dr. WOODCOCK. As I said, right now for peptides, which are related to proteins, very simple peptides are of the same magnitude, of size, and complexity of certain small molecules; and we can approve very short peptides as generic drugs without anything but a bioequivalence trial. Don't forget, even generic drugs ordinarily have a human trial of bioequivalence.

Mr. FERGUSON. But of course that sounds pretty dissimilar from most follow-on biologics which of course as you have said and others have said are incredibly complex?

Dr. WOODCOCK. That is correct.

Mr. FERGUSON. Are there situations where the FDA would not find clinical investigation of immunogenicity warranted?

Dr. WOODCOCK. We feel that for proteins right now we would need clinical testing for immunogenicity.

Mr. FERGUSON. In the absence of any accurate or reliable laboratory or animal model to predict unwanted immunogenicity in humans, how can we be sure that a follow-on protein product which has never been administered to a human being before won't induce some unwanted immune response?

Dr. WOODCOCK. We can't be sure and that is why we need to do testing.

Mr. FERGUSON. OK. In looking at Mr. Waxman's bill, I see a listing of differences between follow-on biologic and innovator that would be required to be deemed to be, quote, highly similar by the FDA. Do you believe that Congress should be telling the FDA in statute how to make these comparability determinations right now given the technology or the information that we have right now?

Dr. WOODCOCK. I think this is a very complicated area that requires some extensive discussion because of the complexity of proteins.

Mr. FERGUSON. Would you be satisfied or comfortable if Congress decided at this moment, given what we know right now, for the Congress to tell the FDA how and when to make these decisions?

Dr. WOODCOCK. I think that——

Mr. FERGUSON. That is a yes or no if you can do it. I am almost out of time.

Dr. WOODCOCK. I can't do it. Thank you.

Mr. FERGUSON. It sounds like you would not be comfortable right now, is that accurate? Would you have other questions, concerns?

Dr. WOODCOCK. We look forward to working with the Congress.

Mr. FERGUSON. She is good, you got to give it to her. She is good. It seems to me there is a major disconnect between the standards that FDA imposes on innovator products and the one that some are espousing that we use on follow-on biologics. There is a big disconnect there. And if we give the FDA authority to approve follow-ons, what agency initiative will be necessary to reconcile these very two different sets of standards if we were to approve something say in Mr. Waxman's bill?

Dr. WOODCOCK. Now, I can't comment directly on the pending legislation. I do believe as I said earlier that the science is going to continue to evolve, and as the Congress contemplates this, they should make room for evolving science because it will change over the decade in a dramatic way; and what we are capable of doing now, which is a lot but somewhat limited in making comparisons, is going to change over time.

Mr. FERGUSON. Thank you very much. I appreciate it.

Mr. PALLONE. I think, Dr. Woodcock, we are going to have to let you catch your breath or something here as we move on. Next is the gentlewoman from California, Ms. Eshoo.

Ms. ESHOO. Thank you, Mr. Chairman. Thank you, Dr. Woodcock, for your testimony. It is instructive and enlightening, and if I am hearing correctly what you have presented both in your opening statement and in your response to the questions that members have posed is, well, several things, but that when it comes to safety and efficacy, it is either in the clinical trial or in the trials that the FDA conducts. Is that correct?

Dr. WOODCOCK. We don't conduct any trials, OK?

Ms. ESHOO. But you require them?

Dr. WOODCOCK. Yes.

Ms. ESHOO. But you require them. Now, my understanding is from what you have said is that there can be an immune response to biologics, and it seems to me that this is a key hurdle because when it comes to biologics that the cure can be worse than the disease, I mean, in the complexity of it.

Dr. WOODCOCK. The proteins are much more prone than the small molecules to cause various types of immune responses.

Ms. ESHOO. Now, if a biotech company notified the FDA that it was making changes to its cell line or its manufacturing process, altering the manufacturing process, what would be the response of the FDA today?

Dr. WOODCOCK. Manufacturers are very well aware before they make any changes to a marketed product, or even a product within the investigational process, they have to get approval from the FDA to make those changes before those products would be used in people.

Ms. ESHOO. All right. Now, if we move to the follow-on biologics that are obviously being proposed with all of the laudable outcomes of broader and more affordable access to them, what do you prescribe as being the process for that? I think that is where the disagreement comes. I really do. I think it is not whether it should happen or not but how to do it, and I think that is the rub of the debate.

Dr. WOODCOCK. Well, I think I can describe what we are doing under 505(b)(2) right, under the Food, Drug, and Cosmetic Act.

And what we do there is the follow-on product is required to submit very, very extensive physical and functional characterization, in other words, laboratory testing comparisons to the innovator product, animal testing of different kinds, and then you have to decide how much clinical testing is needed, depending on how certain you are from all that other work that——

Ms. ESHOO. But you don't believe that there should be a shortcut where the FDA is prohibited from requiring what you just described, if in fact the FDA believes that it should take place?

Dr. WOODCOCK. Many of these products will require additional clinical testing to give you the level of certainty.

Ms. ESHOO. Yes. Let me ask you this. There is a provision that requires the FDA to find a biologic follow-on and the referenced biologic to contain, "highly similar, principle molecular structural features if they are", and I am going to read this because I am not a scientist but I have to rely on the exact language in the proposed legislation, two protein biological products with, "minor differences in amino acid sequence." You have talked about amino acids and what they represent which to me is kind of scary if you fool around with them. Two polysaccharide biological products with differences in post-polymerization modifications, two glycosated protein products with differences in structure between them solely due to post-translational events, infidelity of translation or minor differences in amino acid sequence. This is statutory language. Have you ever seen this before in legislation? Statutory language that is that specific?

Dr. WOODCOCK. It is very specific.

Ms. ESHOO. Well, it is highly specific. Well, you are not going to answer this. I am just going to put this out to my colleagues that are still here. I don't know if you understand this and I don't know if you could all stand by this, but I don't think this is the role of the Congress. I really don't. I think it is up to the FDA to make the call on defining this particular—we shouldn't get into statutory language and be prescribing this.

Mr. PALLONE. Will the gentlelady yield?

Ms. ESHOO. No, because I don't have that much time. I would like to but I can't. I would like to ask you, Doctor——

Mr. PALLONE. Actually, your time has run out.

Ms. ESHOO. Did you include the minute and 2 seconds I didn't use in my opening statement?

Mr. PALLONE. No.

Ms. ESHOO. No? Can I have that?

Mr. PALLONE. It would be better if you did it as a written question. We are going to allow written questions because she is——

Ms. ESHOO. It is just in the European model and maybe someone else will ask that and what——

Mr. WAXMAN. Mr. Chairman, I would like to ask unanimous consent the gentlelady be given 2 additional minutes if she would yield me one of them.

Mr. PALLONE. Is there objection?

Ms. ESHOO. If there isn't, then I will just yield that time to Mr. Waxman because I think Mr. Gordon is going to raise the question about how the FDA views the European model in the follow-on biologic areas. So I will yield the time to you.

Mr. WAXMAN. Thank you very much. Just on that one point where we spell out in my bill this language about deeming certain molecules, that is from an FDA reg and it is not spelling out a broad universe, it is narrowing the universe of possible follow-through drugs, and then once you narrow it, then they have to meet the second standard in the legislation which is that it is just clinically significant—no clinically significant differences in terms of safety. So it is not deeming something to be a generic, it is narrowing all the different fields to make sure it is a good candidate to be a follow-on biologic but we still require FDA to use that very strict test in your scientific judgment whether it

Ms. ESHOO. Yes, can I just jump in here since I yielded you?

Mr. WAXMAN. She is shaking her head yes.

Ms. ESHOO. You are still saying it is a regulation, though?

Mr. WAXMAN. Are you saying yes for the record? Am I correct?

Dr. WOODCOCK. That is correct. See, in the original Hatch-Waxman, you used the term same active ingredient. That doesn't apply here because as we have discussed extensively, they are not exactly the same. So the question arises, what actually would be a candidate for being considered under some scheme? How close does it have to be? That is the question.

Mr. PALLONE. OK. Time is expired, and we move to the gentlewoman from Tennessee.

Mrs. BLACKBURN. Thank you, Mr. Chairman. Dr. Woodcock, you have been so patient and as you can tell, we are not scientists and researchers but we all want to be certain that new protocols and new therapies have the ability to make it to our patients, and we want to be certain that there is a fairness applied to this entire process as we look at the follow-on process.

Let me come at this from a different angle. In my opening statement I mentioned to you intellectual property concerns, and I have thought, reading your testimony and we appreciate that coming forward to us and then I also have a May 5 report from CRS on the follow-on biologics that I have done a little bit of reading on. So let us take it this way. You have got the applications for approval of biologics, and these contain trade secrets, correct?

Dr. WOODCOCK. Yes.

Mrs. BLACKBURN. OK. And when you render a finding that a biologic is safe, pure, potent, you are relying in part on that trade secret data, correct?

Dr. WOODCOCK. Yes.

Mrs. BLACKBURN. OK. So explain to me how you think you can rely on the finding of one biologic to approve a second or similar biologic without using that trade secret data and without compromising that intellectual property which I see as a private property right.

Dr. WOODCOCK. We don't have that ability now under the PHS Act and so we do not approve follow-on proteins under the PHS Act. Under the Food, Drug, and Cosmetic Act, the scheme that was set up under Hatch-Waxman allows FDA to rely on the fact of approval of prior products, and that is how we do it. We do not rely, we don't go in and look at the data when we approve all these generic drugs.

Mrs. BLACKBURN. So then you feel as if you are doing that without exposure to the person that is the creator or the intellectual property holder of a specific trade secret?

Dr. WOODCOCK. Well, obviously I probably don't understand your question fully. To my understanding, Hatch-Waxman set up kind of the balance between the protection of the innovator for a certain amount of time, patent extensions and so forth, and then the ability at the end of that for copies to come in and the FDA to have the ability to approve copies.

Mrs. BLACKBURN. OK. I thank you for that. I think that for some of us that represent so many individuals that work in the innovative and creative community if you will, and in our State of Tennessee as we see a biotech industry that is beginning to grow, we look at lessons learned and places that we can go for lessons learned. Much of that is through our creative community, through our songwriters, through our auto engineers, people who have seen copyright infringement, who have seen intellectual property violations. And it raises a specific concern and a guard, and they highlight that with us that there is concern there that it is a very fine line, it is a very complex issue, and that we have to step very, very carefully.

Following on with that, would you say yes or no, are we jumping the gun to try to create a follow-on pathway? Are we trying to get ahead of ourselves as Congress, as legislators?

Dr. WOODCOCK. Well, I have said, FDA has approved some follow-on products where we have a pathway available. So obviously FDA believes that this is possible. It is possible to approve certain follow-on products. A pathway is not available under Public Health Service Act, so that balancing that you refer to, the innovation and need for innovation and the need for affordable treatments is something only I think the Congress can deal with.

Mrs. BLACKBURN. OK. Thank you. I yield back.

Mr. PALLONE. Thank you. The gentlewoman from Illinois, Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Dr. Woodcock. This is not an area where I have any sort of expertise, so let me ask some very basic questions.

Recently you testified at a House Oversight and Government Reform hearing that the negative immunogenicity's response from Eprex may have only been discovered in a 50,000-person clinical trial. Has a pharmaceutical manufacturer ever submitted a safety study of this size?

Dr. WOODCOCK. That is a good question. Possibly of that magnitude. That is a very, very large study and so would be very unprecedented.

Ms. SCHAKOWSKY. So it is not common?

Dr. WOODCOCK. No.

Ms. SCHAKOWSKY. So if not, then what types of tests could have been conducted to provide FDA with relevant safety information for this drug or others like it?

Dr. WOODCOCK. There is a wide-variety of laboratory tests that can be done and animal tests to look at things like immunogenicity, and limited human studies can be done. However, with most rare drug side-effects, which would require 50,000, 100,000, 1 million

people to be exposed, to find them we use post-marketing to evaluate that because all drugs have rare side-effects sometimes that are serious and to require them before the drug would be put on the market would mean we basically wouldn't have any drugs available to people. So we need a robust post-marketing safety system to find these things so that we can learn about them.

Ms. SCHAKOWSKY. So you again have to figure out the balance of what you do pre-marketing and then if it is a cost benefit sort of thing?

Dr. WOODCOCK. Yes, however, let me say that that is not the only kind of immune response that can be negative. You can have a very common immune response to a protein that can have an adverse affect, and that could be picked up in a small trial. So it really depends on what you are looking for.

Ms. SCHAKOWSKY. OK. I know that the ranking member asked about different batches and whether they could be the same but I wanted—but most comparability decisions are confidential, there is one involving the biotech drug Avonex, that is public, and I am wondering if you could tell us a little bit more about what kind of changes the FDA permitted in that case without repeating—and this is a follow-on used to treat relapses of MS and it is made by Biogen which is a generic company as you know—what kind of changes the FDA permitted in that case without repeating the original safety and effectiveness trials?

Dr. WOODCOCK. Right. Those changes included manufacturing site, the cell line, and they were very, very extensive changes that were done; but very extensive characterization was done to assure comparability of those two molecules.

Ms. SCHAKOWSKY. But it did not require the repeating of the original safety and effectiveness trials?

Dr. WOODCOCK. That is correct. Now, the second manufacturer had access to quite a bit of the data about the manufacturing process and so forth that was originally done.

Ms. SCHAKOWSKY. There are several biologics that are regulated under the Food, Drug, and Cosmetic Act that have been approved based on abbreviated data; and I believe the FDA provided a letter to Chairman Stupak and Chairman Dingell in February citing these examples. And in some cases low complexity products, that is what you have been talking about, the short, have been rated interchangeable. So the FDA has already demonstrated that it is possible to approve at least some biologics based on abbreviated data and even make interchangeable decisions. Am I just basically repeating what you have already said?

Dr. WOODCOCK. Yes, the interchangeable decisions were for peptides, and they were very, very small versions of protein that are more like a small molecule drug. We have not approved any proteins really under the (j) process, any recombinant proteins.

Ms. SCHAKOWSKY. And I also have a question that I am curious what the FDA views as the appropriate level of discretion in this decision-making process. I guess you get back to you want to work with us?

Dr. WOODCOCK. Yes.

Ms. SCHAKOWSKY. I thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Dr. Burgess.

Mr. BURGESS. I guess that statement is the key point, and we do clearly need to work together on this. Let me just ask you on some of the stuff we have heard this morning and your written testimony, the parts you make about the hyaluronidase that required the additional testing because of allergic reactions because of its recovery from the tissue, if you end up having to do all of that, are we still going to see price savings in the product when it is delivered?

Dr. WOODCOCK. Well, obviously there is a debate about that. However, it is the large-scale clinical safety and efficacy studies that are the very expensive part of development, as well as the R&D that goes into producing the innovation in the first place. So there would be reduced costs to producing a follow-on because you wouldn't have to do the original research and you may not have to do the clinical efficacy studies. However, it wouldn't be of the same magnitude of reduction of cost of development that you would have for a small molecule.

Mr. BURGESS. But in doing so, and I think Mrs. Blackburn already addressed this, said in doing so, do you not out of necessity have to use some of the proprietary information from the original manufacturer?

Dr. WOODCOCK. Under the 505(b)(2) process we do not go into the originator application and look at anything, but we know we approved it so we are relying upon the fact of the approval.

Mr. BURGESS. So the fact of approval, is it the public domain and not proprietary information?

Dr. WOODCOCK. Right. Yes.

Mr. BURGESS. Do you have any thoughts with all of the questions you have been asked this morning in your extensive testimony which we all appreciate, have you any thoughts about how we go about minimizing uncertainty for the FDA in this rather complicated new world that we find ourselves in?

Dr. WOODCOCK. Well, I agree that there need to be extensive discussions and we look forward to working with the members.

Mr. BURGESS. Do you have any thoughts as to how we on this side of the table, not this side of the aisle, but how we can give you the flexibility that you are going to require in order to make room for this evolving science?

Dr. WOODCOCK. Well, for example, we feel probably that under 505(b)(2) we do have a great deal of flexibility the way that program has been implemented over the years, and we will have approved follow-ons that have had extensive clinical trials and we approved, for example, the hyaluronidase that simply had a immunogenicity trial. Although hyaluronidase is a very complicated protein. It shows the spectrum of things that can be done under that scheme, under that pathway.

Mr. BURGESS. Now, have there been products that you thought initially this shows a lot of promise for follow-up biologic that you have had to pull back and require additional testing? Some of the things that you mentioned earlier, the change of the filter, the change of the atmospheric pressure outside when you filter the compound, the change of a stopper composition that would perhaps be different from one lab to another?

Dr. WOODCOCK. Right. Well, for the more complicated proteins, those issues pertain to manufacturing. Say if the manufacturer wants to change sites which happens sometimes, or open up a new site. Then all those factors from environmental factors all the way to how the production process is done have to be looked at very carefully to make sure they are making the same product, and that is the same manufacturer.

Mr. BURGESS. Even under the original manufacturer?

Dr. WOODCOCK. Yes.

Mr. BURGESS. That is even before you get into a follow-on situation?

Dr. WOODCOCK. Yes, we have a lot of experience in regulating all these manufacturing changes because some of these products, for example, become very successful and additional production capacity, scale up, new plants and so forth have to be opened. And in those cases, the manufacturer has the burden of showing that the molecule they are making in there will perform the same as the original one.

Mr. BURGESS. Let me ask you, if we do this legislation, are the people who work at the FDA, the people who are tasked with ensuring that our Nation's drug supply is safe and effective, do you detect any concern on the part of the staff of the FDA that they are going to be under any pressure to deliver these products before the testing is actually complete? Mr. Green referenced Ketek and the Vioxx situations. Are we setting ourselves up because this is inherently more complicated than a Ketek or a Vioxx? Are we setting ourselves up for that? Let me just ask you it this way. Do you detect concern among the staff, the career people at the FDA, that we are tasking them with something that is virtually impossible?

Dr. WOODCOCK. I think as I said we have the technical, scientific, and medical expertise necessary to make these decisions. We require adequate resources to do that, and obviously if a new statute were passed, it would have to be sensible. It would have to take all the parameters that have been discussed today into consideration so that it could be implemented properly.

Mr. BURGESS. But again, are you detecting any undercurrent from the staff that there is going to be—we are the ones that are going to have oversight over that. You see the level of expertise that we present today. You guys are the experts. Are you detecting concern from the experts within the FDA itself about how this is going to be regulated?

Dr. WOODCOCK. I think the experts' concern only is that we need to have access to resources in the ongoing scientific expertise that would enable them to make these decisions.

Mr. BURGESS. Mr. Chairman, you have been very kind, and I realize that means we have a vote. I mean, I think it is so important that we give you the flexibility and you look back to the days when Sir Alexander Fleming discovered penicillin, it was more of a parlor trick that he was able to inhibit bacterial growth in a Petri dish, and it wasn't until somebody figured out the manufacturing process that made it clinically useful. The same could be said for cortisol, that after it was derived it was very, very difficult to come up with amounts that would be clinically useful until that manufacturing process came about. So we are kind of on the cusp of that type of

change in medicine right now. It is so important that we get it right. I think we were read a passage from the bill, and the part about the two similar saccharide repeating units, even if the number of units differences, and there are differences of the post-polymerization modification, saccharide being sure and basically we are talking about the difference between cane syrup or cellulose or a celery stock and you can see you could end up with a completely different product that will have a completely different intent. We have to be so careful as we go through this, Mr. Chairman.

Mr. WAXMAN. OK. Let me yield.

Mr. BURGESS. I would be happy to yield to my friend.

Mr. WAXMAN. I think your line of questioning is very thoughtful and got right to the nub of it. Dr. Woodcock, you do have this 505(b)(2) authority now which gives you all the flexibility. If we had the same kind of provision giving the FDA the same level of flexibility to require whatever you need without any deadline to approve a drug, not approve it at all until you reach that conclusion that it is just as safe and effective, would that be sufficient authority for you?

Dr. WOODCOCK. I——

Mr. WAXMAN. You already worked with that.

Dr. WOODCOCK. I really can't comment. I can say that we are approving drugs under that pathway right now, and that has flexibility. It doesn't have some of the issues that pertain to all the biological products that are now approved and have not been under this scheme.

Mr. PALLONE. There is no time left, and I have got to figure out what we are doing here. We have 11 minutes before the first vote. This is a 15-minute vote followed by two 5-minute votes. I wouldn't be that long, so I am hoping you can wait for us to come back because we have another three or four members that would like to ask questions, OK?

Dr. WOODCOCK. I would happy to do so.

Mr. PALLONE. Thank you. But maybe we will get in—let me—there is a 15-minute vote of which there is 11 minutes left and then two fives. If you would like to ask your questions, Mr. Gordon, we can do that now? I just want the Members to know after Mr. Gordon we will vote and come back.

Mr. GORDON. Dr. Woodcock, you are doing a good job. If you were my chemistry teacher, I think I might have amounted to something.

Let me ask you one question. It is my understanding that the Europeans have already started a process for follow-on biologics. Could you tell us what they are doing, what you think are the pros and cons, and how it is similar, dissimilar to what is happening here?

Dr. WOODCOCK. I think we have to realize that Europe has a somewhat different setup and scheme than the United States, so it is not really strictly extrapolatable to here. However, in Europe the plan is that the EMEA, the medicines regulatory agency will make these decisions. They did not have the distinction between a Public Health Service Act and a Food, Drug, and Cosmetic Act. These products were all under their ordinary scheme already.

They have a program called Biosimilars, and for Biosimilars the Medicines Agency will construct a guidance for each product area and will put that guidance out and then submissions can come in that conform with the guidance. We work very closely with the Europeans, the EMEA, and we are quite aware of what they are doing. And their approach to Omnitrope for example is very similar to the approach that we took subsequently.

Mr. GORDON. Do you have an opinion as to the pros and cons of what they are doing?

Dr. WOODCOCK. I don't know that their approach is, as I said, directly applicable to here in the United States. However, I think they are using good science and a public process to move forward.

Mr. GORDON. Thank you. You represent your agency very well.

Dr. WOODCOCK. Thank you.

Mr. PALLONE. Thank you. So we will now be in recess until after these three votes, and then we will come back and you will wait. Thank you, Doctor.

[Recess.]

Mr. PALLONE. We are back in business. The gentleman is recognized.

Mr. INSLEE. Thank you. Dr. Woodcock, I wanted to focus on the issue of clinical trials, the advisability of that. It is important. My mother was an insulin-dependent diabetic, my brother is an insulin-dependent diabetic, I am going to be in a race with 5,000 insulin-dependent diabetics here in a couple of weeks and I would like to tell them if we come up with a biologic that it is going to be safe and we can have confidence about that. I want to make sure I understand. You are of the belief at this time given the present state of scientific knowledge that it is important to have some level of clinical trials for follow-on biologics to prevent unwanted immunogenicity.

Dr. WOODCOCK. That is correct, and in some cases we may need additional clinical trials, if there are additional things that we aren't certain about.

Mr. INSLEE. Now, you have also alluded to the potential that there might be scientific advances to obviate the necessity of clinical trials. You made some reference to that. So I just wanted to ask you about that. Can you give us with a reasonable degree of certainty that in fact that will happen for all of these drugs?

Dr. WOODCOCK. No. I believe that the science of characterization will advance over time, and therefore we will be able to do better and better comparisons in the laboratory and functional comparisons and so forth so that we will have less uncertainty about how similar they are. We will be much more sure about how similar they are. That doesn't mean though that we will be able to completely rule out clinical trials.

Mr. INSLEE. Could you say that in the next 5 years most follow-on biologics scientific knowledge would advance so that you would not require clinical trials for most incidents?

Dr. WOODCOCK. No, I think the opposite is true. Over the next 5 years, we would need clinical trials of some sort for most proteins, follow-on proteins.

Mr. INSLEE. I and others have introduced a bill that would have a statutory requirement for some level of clinical trials, and frankly

for the reason it is sort of like seatbelts. We have requirements for seatbelts. There may be science developed some day that we get arround airbags or some other, but the best science we have right now we require seatbelts and that is an appropriate legislative decision. So I am asking, I guess is there any reason why we should be the first country to not require clinical trials in these contexts?

Dr. WOODCOCK. I think from the FDA standpoint, we would require clinical trials, say, under the 505(b)(2) whenever they are necessary, and right now they are going to be necessary for almost every protein. In the future, they may not be necessary for some category of proteins. Right now, for example, for very short peptides which are very tiny versions of proteins, we don't think we need clinical trials other than perhaps the bioequivalence type of studies, it would be done for a generic drug.

Mr. INSLEE. If Congress does require clinical trials on a bill similar to mine or others, would there be any damage to the pace of scientific inquiry by doing that? Is there any downside in that regard?

Dr. WOODCOCK. I think it would depend on how specific you were or how proscriptive you were. There are many kinds of clinical trials, everything from bioequivalence trials that mainly look at the pharmacokinetics of a drug to a codynamic trial, safety trials, efficacy trials. Each of those have different ramifications. So we think right now that we would probably need in most cases immunogenicity trials as well as probably human pharmacokinetic trials.

Mr. INSLEE. And I think if you ran by your opening statement, you would find that you pretty much described the bill that I had introduced as far as giving you that level of flexibility to determine which ones that would require some clinical trials. And I for one believe it is appropriate for Congress to set some level of protection. We have done this in various contexts in the Food Quality Protection Act. We established actually numerical requirements for pesticide residues. In the 1996 Safe Water Drinking Act they had numerical standards for lead, mercury residues and we thought that that was appropriate. Could you tell us with any more degree of certainty at all to characterize when you think science probably will obviate the necessity of clinical trials? Can you give us any greater certainty as to time, this decade, the following decade?

Dr. WOODCOCK. As I said in the last hearing, I think within this decade we will be able to characterize some of the very, very simple proteins well enough that we probably will be able to decide that they are similar enough to an innovative product. That is within this decade. But there are many other complicated products that are very important products that I think we would still not be able to do them in the next 10 years.

Mr. INSLEE. So I guess what you are saying we are dealing in probabilities here. You think there is some probability that within this decade some of the simpler proteins may be categorized without this, but the bulk of them and the more complex ones would not in this decade, is that a fair assessment?

Dr. WOODCOCK. That is my prediction but I don't have a crystal ball.

Mr. INSLEE. Well, I thank you very much. Take care.

Mr. PALLONE. Thank you. I think we are out of questions. Thank you, Doctor. I really appreciate your testimony and bearing with us through the votes and all that.

Dr. WOODCOCK. I am happy to do so.

Mr. PALLONE. And we may send written questions to you within the next 10 days or so for you to respond to.

Dr. WOODCOCK. We would be pleased to do that.

Dr. WOODCOCK. Thank you.

Mr. PALLONE. And now we will have the second panel come forward.

Welcome. Thank you for being with us today. I am just going to introduce everybody with their titles here. First is Dr. William Schwieterman who is from Tekgenics in Mobile, Alabama. Next is Dr. David Schenkein, vice president, clinical hematology/oncology at Genentech from south San Francisco; Dr. Geoffrey Allen, president, CEO, chairman of Insmed Incorporated from Richmond; Mr. Richard Kingham who is a partner in Covington & Burling here in DC; Mr. Bruce Downey who is chairman of the board of the Generic Pharmaceutical Association, actually from Woodcliff Lake, New Jersey; and then we have Ruth Hoffman, executive director of the Candlelighters Childhood Cancer Foundation from Kensington, Maryland; and Dr. Ed Weisbart who is the chief medical officer for Express Scripts from Maryland Heights, Missouri.

Thank you for being here today. We have 5 minutes' opening statements, and if you would like to submit some additional information for the record that is pertinent, we will also allow that and we will start with Dr. Schwieterman.

STATEMENT OF WILLIAM SCHWIETERMAN, M.D., TEKGENICS, INC., MOBILE, AL

Dr. SCHWIETERMAN. Thank you very much, Chairman Pallone, and good morning members of the Subcommittee on Health, Energy and Commerce.

My name is Dr. William Schwieterman, and I thank you for the opportunity to appear before the committee today and present a scientific and clinical perspective on the issue of biogenerics.

One of the most disturbing experiences for a physician is to know that a treatment is available to help your patient but the cost may simply be beyond what your patient can afford. Sadly, this is what many patients who need treatment with brand biopharmaceuticals are facing in today's world. For this reason, I strongly believe that Congress must give FDA the authority it needs to create a workable, scientifically based abbreviated approval pathway for biogenerics and given that I also had the privilege of working at FDA in the area of biotechnology for 10 years, I know that this can and should be achieved.

I was heartened to hear during the House Oversight and Government Reform Committee in hearing that the FDA Deputy Commissioner Janet Woodcock also believed that this goal could be achieved, stating that the FDA can be trusted to carry out its mandate from Congress, whatever that might be and the long-anticipated FDA white paper recently released by FDA also validates their ability to prove biogenerics for efficacy and safety.

I come before you today wearing three hats, as a physician, as a scientist, and as a former FDA reviewer. From this vantage point, I would like to make the following critical points. First, with today's scientific advancements in technologies, FDA can assure the safety and efficacy of biogenerics. Second, the supporting science for this is not new. It has existed for over a decade. The FDA white paper confirms that FDA has already been using a science-based approach case by case to approve biopharmaceuticals and more importantly changes in biopharmaceuticals. Third, the issues raised in post-approval brand product changes are reflective of the issues that are raised with biogenerics. In other words, the same science that determines comparability for the brand to biotech industry can also be adopted to ensure the safety and efficacy of comparable and interchangeable biogenerics. This point is particularly important when it comes to the issue of conducting clinical trials.

As Dr. Woodcock noted at another House hearing, it is a common misperception that clinical trials are always the most sensitive studies for detecting changes in safety or effectiveness due to process changes. I agreed with her when she went on to state, "Where trials aren't needed, it is of questionable ethics to repeat them, so use of human subjects for trials that are not needed that are simply to check a box on a regulatory requirement are not desirable." The necessity and type of clinical trials required for biogenerics should be determined based only upon a scientific standard established by FDA on a case-by-case approach. Having worked extensively at FDA with many physicians and scientists and listening to the words of Dr. Woodcock and other FDA officials these past few months, I also want to emphasize there is just one safety standard at FDA and that standard has been and will continue to be applying the review and approval of each and every biologic, whether it be brand or generic. It is relevant to note that the standards and science used for current biopharmaceuticals are informative for us with respect to generics. A critical but not often publicized fact about the biopharmaceutical industry is that FDA does not require brand companies to perform large clinical outcome studies to retest the product generated by new manufacturing processes. This is because such an approach would not only be infeasible but more importantly would ignore the utility of existing sophisticated scientific analytic tools and techniques for this purpose.

Let me briefly summarize what happens in these instances. FDA starts with an assessment of extensive analytic comparability data. With these data, and keeping in mind the nature of the drug, the test used, and the disease being studied, FDA decides how to proceed. The agency can give a thumbs up and a thumbs down regarding each post-approval brand manufacturer change and if thumbs up, have that change be supported by analytic data coupled with pharmacokinetic or pharmacodynamic studies or the studies just mentioned, plus data from a large clinical outcome study.

It should also be noted the vast majority of brand manufacturer changes need no further studies when data from analytic tests show the product to be comparable. For a small number of brand products that show small differences in analytic tests for following manufacturer change, FDA may require additional analytic and

pharmacokinetic or pharmacodynamic tests to be conducted in animals or humans.

The latter studies are clinical studies in the sense that they are conducted in patients in the clinic but they are not the large outcome studies commonly used to determine the product's ultimate clinical effects. These pharmacokinetic and pharmacodynamic studies almost always involve fewer than 100 patients and last weeks, not months. Rarely after a brand manufacturing changes the FDA required that a brand company take the last step, repeating a full-scale clinical outcome study. In fact, of all the hundreds of brands of biologic products changes, the vast majority were approved without large clinical outcome studies.

In sum, FDA scientists and physicians routinely make comparability determinations between similar biologic products since manufacturing changes occur throughout the brand biologic product development life cycle. The scientific essence and basis of comparability determinations used by FDA is therefore not new but rather has existed for over a decade to allow brand biologic manufacturers to change and improve their manufacturing processes.

The Access to Lifesaving Medicines Act will give the FDA the authority and flexibility it needs to ensure the safety and efficacy of biogenerics. It adopts the same scientific principles, processes, and procedures that exist for the brand biologic industry when making post-approval manufacturing product changes in the biogeneric sector.

I would like to emphasize the need for science——

Mr. PALLONE. Doctor, if you could summarize because you are over the 5 minutes.

Dr. SCHWIETERMAN. Thank you. A truly workable pathway for biogenerics is one that that is fully scientifically based, consistent with regulatory experience, and brings safe and effective biogenerics to patients in a timely manner. Thank you so much.

[The prepared statement of Dr. Schwieterman follows:]

William Schwieterman, M.D.
Testimony before the House Energy and Commerce Subcommittee on Health
Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States
May 2, 2007

Good morning Chairman Pallone and members of the Subcommittee on Health. My name is Dr. William Schwieterman, and I am pleased to come before you today to present a scientific perspective on the issue of safe and effective biogenerics and the need for a corresponding pathway. But before I do, I want to thank Congressman Pallone and the other distinguished members of this Committee for the opportunity to testify on this important public health issue.

I know that the members of this Committee have been committed to ensuring greater public access to affordable medicines. It is fitting that you are now seriously exploring the need to expand access to today's biopharmaceutical medicines. As a physician, I know only too well that we as a society need to continue to foster medical and scientific research, while also ensuring that patients have access to safe, effective and affordable medicines. Today, patients are benefiting from biopharmaceutical therapies, but they can only benefit from them if access is not a barrier. Unfortunately, access to biopharmaceuticals is often hindered by their high costs and affordability. This is a growing problem as the medical benefits of both new and existing therapies expand into many therapeutic areas. For these reasons, I deeply share the goal of those who are working to create a sound, scientific – based workable abbreviated approval pathway for biogenerics – one that allows the FDA, the scientific and medical flexibility it needs to approve safe, pure and effective biogeneric medicines.

I. Introduction

By the way of background, I am a physician-scientist with training and medical boards in internal medicine, sub-specialization in the field of rheumatology, and scientific training in biotechnology and immunology.

Following my initial clinical training, I worked for 5 years at the National Institutes of Health. During my NIH tenure, I worked with children with congenital immune disorders for three years at the National Cancer Institute, providing clinical treatment while simultaneously performing molecular biology research (gene mapping) in an effort to identify the underlying patient genetic disorders.

I also worked at NIH's National Institute of Arthritis and Musculoskeletal Skin Diseases garnering significant scientific and medical expertise in the fields of clinical rheumatology and cellular origins of systemic lupus erythematosus.
I subsequently joined the U.S. Food and Drug Administration, where I worked for ten years within the Center for Biologics Evaluation and Research in the Division of Clinical Trial Design and Analysis. I became Chief of the Medicine Branch

within this Division, and later became Chief of the Immunology and Infectious Disease Branch. In these roles, my primary responsibilities focused on outcome clinical trial design, which assesses the design of clinical development plans for novel investigational biologic agents to elicit meaningful data on product safety and efficacy. Relevant to today's discussion, I supervised for a decade outcome clinical studies and corresponding brand biopharmaceutical approvals in the areas of neurology, cardiology, rheumatology, infectious disease, organ transplantation, among others.

For the last five years, I have been an independent consultant to the brand biopharmaceutical industry. I currently work with major innovative biopharmaceutical companies, many large pharmaceutical companies, a number of start-up firms and recently entities interested in biogenerics. In this capacity, I provide scientific and medical advice on investigational new drug product development, primarily directly related to establishing the safety of efficacy of these agents.

Over the course of my career, I have witnessed first-hand the evolution and development of biopharmaceuticals as powerful agents that are transforming many fields of medicine, as well as increasing the longevity and quality-of-life of patients. To this day, I find the power and potential of biopharmaceutical medicines to be astonishing. I believe that this period of time may certainly be remembered as the birth of a new era in medicine -- an era that will be remembered if only we can expand patient access to these promising new drugs. This is why I believe the passage of the Access to Live-Saving Medicines Act (ASLMA) is so important. This legislation would result in greater access and meaningful savings to patients by stimulating investment in new, and more critical biopharmaceutical agents while also providing generic competition that will certainly lower health care costs.

In my testimony today, I will make the following public health, scientific and medical points:

• FDA has one approval standard for both brand and generic drug products. Each and every biopharmaceutical must be deemed to be safe, pure and effective for their intended use before FDA scientists and physicians will approve the product.

• The science to support biogenerics has existed for a decade. This science has advanced, and has been utilized by the brand biopharmaceutical industry in the form of FDA's Brand Biopharmaceutical Comparability Approach to support post-approval brand product changes.

• Permissible post-approval brand product changes can fall into one of three categories, with all three requiring multiple analytical tests and

assays and which may be supplemented by animal data and other supporting data in the following list of prominence and sensitivity:

* Human Pharmacokinetic Studies
* Human Pharmacodynamic Studies
* Human Clinical Outcome Studies

• Adoption of this comparability approach to biogenerics is scientifically sound, and FDA should use a case-by-case approach for determining the appropriate approval criteria for biogenerics – just as it said in a recent White Paper that it has been doing with brand biopharmaceuticals.

• Science and medicine can clearly support the approval of many safe and effective comparable and interchangeable biogenerics today.

II. The Science Behind Patient Safety & Product Efficacy

Despite what others in this debate may have implied, biogenerics can and will be safe for patient use and may be therapeutically interchangeable. I say this because the opposition completely ignores the FDA's scientific and medical prowess in this debate - the same prudent, accomplished and proficient skills used every day by agency officials to approve brand biopharmaceuticals will be used to approve biogenerics. And having worked with agency physicians and scientists for over 10 years, it is clear to me there is just one agency safety standard. And that standard has been, and will continue to be applied in the review and approval of each and every biologic – whether it be a brand or generic.

In March, I had the honor to testify at the same hearing as FDA Deputy Commissioner Janet Woodcock. At that hearing, my former colleague agreed that the science exists for FDA to approve safe, effective and affordable biogenerics. Dr. Woodcock's responsibility, and the responsibility of all FDA staffers, is to ensure safety. When I was at the FDA, my primary responsibility was to ensure the safety of new biopharmaceuticals.

To ensure safety, the FDA uses many tools across many disciplines including, sophisticated analytic techniques, manufacturing controls, pharmacokinetic and pharmacodynamic assessments in short-term patient studies, and longer-term clinical outcome studies. It is important to understand that the sophistication of these tools is constantly increasing, as is the corresponding experience level of staffers involved in the review process. As a result, these capabilities are more robust and effective than ever before, and the FDA uses these tools everyday from product development to post-marketing approval issues.

Furthermore, product development review at the FDA is a dynamic process - not a static one. The FDA actively learns from the data generated by these tools, to

identify and design future phases of product development and post-approval requirements. Especially by the end of product development of a biopharmaceutical agent, a large amount of information regarding the clinical efficacy of a biologic molecule as it relates to its structure and pharmacology, is necessarily understood. This knowledge base forms the foundation of product information prior to market approval. And this foundation is substantially enhanced by the extensive product marketing history upon which the FDA can effectively structure the appropriate abbreviated approval criteria for specific biogenerics.

i. Understanding the Science of Comparability &
The Brand Industry Experience: Post Approval Product Changes

At the heart of the legislative biogeneric debate is the soundness of the science to ensure biogeneric safety and efficacy. In particular, questions are being raised by some regarding the appropriateness of the scientific principles of comparability; and whether, as some have argued, large clinical outcome studies are a critical requirement for an appropriate regulatory pathway for biogenerics. Yet, we need only to examine closely the extensive and vast biopharmaceutical industry experience over the last decade and more to scientifically reject these questions.

The science of comparability determination is one that requires both judgment and expertise. The data generated by the scientific tools must be assessed according to its strength, reliability and relevance to the ultimate safety and efficacy of the product. And hence, determining comparability does not rest on a single test, or even a given set of multiple tests. Rather, it involves a step-wise approach that builds upon what is learned in previous tests and on the nature of the biopharmaceutical agent in question. And at the very heart of FDA's comparability approach is product characterization and other tools which ensures the safety of drugs and biopharmaceuticals, with product characterization techniques being the scientific underpinning of this endeavor. The underlying scientific principle, as the FDA aptly noted in the agency's Congressional testimony of June 2004, the greater the comparability between two protein products, the greater the confidence that their clinical performance will be the same.

Of great interest is the fact that scientific advances allowed the agency to adopt and apply comparability principles to approve brand biopharmaceutical postapproval changes over fifteen years ago. These scientific principles not only allow for insignificant post-approval brand product changes, but also very significant manufacturing changes, such as cell-line replacements, manufacturing facility site changes and the like. Contrary to what others may say, the scientific evidence has not required the vast majority of post-approval brand product changes to be supported by large clinical outcome studies. Instead, the FDA has used, and continues to use, a well-grounded and validated scientific-based

comparability approach to approve these changes – a process that employs sophisticated and advanced analytical tools to assess chemical, physical and biological function of biopharmaceutical agents. These analytical tools have been, and will continue to be buttressed by human pharmacokinetic, human pharmacodynamic, animal studies; yet, rarely, clinical outcome studies. Let me explain.

a. Comparability – Manufacturing Changes

FDA's drug approval process is dynamic. Once a brand biopharmaceutical product is FDA approved for therapeutic use, the manufacturing process often changes. Likewise, new manufacturing plants are built, more efficient processes are incorporated into the manufacturing scheme, new materials are used to generate the drug product, and so forth. These changes are not only inevitable, but welcomed by the FDA, since they often lead to both safer and more efficiently produced drug products.

To facilitate and encourage changes in manufacturing, the FDA does not require a new clinical outcome study to be conducted each time that there is a change. That is, the FDA does not require each time that a large number of patients over a long period of time be re-tested for clinical outcomes to ensure that the product generated by the new process is the same as the old process. Such an approach would not only be infeasible, but would ignore the utility of existing analytic tools used to test for comparability between agents.

In fact, Dr. Woodcock stated firmly to the House Committee on Oversight and Government Reform that is a common misperception that clinical trials are always the most sensitive studies for detecting changes in safety or effectiveness due to process changes. She went on to state and I quote, "**Where trials aren't needed it is of questionable ethics to repeat them. So use of human subjects for trials that are not needed, that are simply to check a box on a regulatory requirement, are not desirable.**"

The existing paradigm at the FDA for manufacturing changes does not rest on large clinical outcome trials, or on licensing of specific manufacturing sites. The former are too expensive and cumbersome, not to mention insensitive, to detecting small differences in clinical outcomes. The latter requirement was eliminated in the early 1990s with the adoption of Comparability Principles. So what happens at the FDA when such a post-approval brand product change occurs? The FDA employs scientifically grounded, comparability principles to assess these changes.

As Dr. Woodcock told your House colleagues, " manufacturing changes and process changes are undertaken for all pharmaceutical products, whether drugs or biologics. And in each case, we have to determine whether or not the change could

result in any clinically significant change in the product, whether it's a small molecule or whether it's a large, complex molecule of some kind. And FDA has a long history of quality regulation, putting into place the procedures, both physical characterization of the new product and comparing it to the old product, functional characterization of the new product compared to the original product, and sometimes clinical characterization of the new product."

Let's assume for sake of discussion that two biologic products have been produced by the same brand company using different manufacturing schemes. First, the biologics are analyzed for structural, chemical and biological differences using a suite of analytical techniques, including peptide mapping, chromatography, and electrophoresis. In other words, multiple techniques and assays are conducted in a step-wise approach to determine comparability between different manufacturing schemes, built upon what is learned in previous tests and on the nature of the biopharmaceutical agent in question. And, analytic tests are always first performed with any product characterization following a manufacturing change, since these tests form the bedrock of product.

Of course, the critical analysis of this exercise is to determine that the product generated from a changed manufacturing scheme is as safe and effective as that demonstrated by the original product. If significant differences between the two products are noted within and among these tests and assays, the agency's review process could effectively stop. The new product from the new manufacturing scheme may be declared "insufficiently similar" to the original product. In such cases, the biologic sponsor is required to essentially start the R&D/manufacturing process all over again.
If the new biologic product from the new manufacturing scheme shows identity/comparability or perhaps slight or minor differences between it and the original product, the FDA will make a scientific assessment. Specifically, the FDA will decide if the amount and type of data they have, from the tests used for the biopharmaceutical agent and clinical use under discussion, are adequate for determining comparability, of if more analyses or assessments are needed before full assurance of comparability can be made.

For the vast majority of manufacturing changes, there may be no need for further studies of any sort when data from analytic tests show the products to be comparable. Even when these tests show small differences between two batches of the same brand biologic, the FDA often determines that there is no need for additional product characterization since these small differences are deemed insignificant to ultimate clinical safety and efficacy.

However, for a limited number of biologic products that show small differences on analytic tests following manufacturing changes, additional analytic tests and perhaps short-term assessments of the pharmacokinetics (assessing blood levels in various tissues) and pharmacodynamics (assessing the short-term impact of the agent on laboratory parameters) may be required in animals and/or

humans.

The latter studies are clinical studies in the sense that they are conducted in patients in the "clinic." But they are not the large and protracted studies commonly used to determine the product's ultimate clinical effects. These pharmacokinetic and pharmacodynamic studies almost always involve fewer than 100 patients and last weeks, not months.

Rarely does a brand company have to repeat a full scale clinical study to ultimately answer the question of comparability. In fact, given the variability and "noise" involved in most clinical outcome studies, it's often very difficult to use these studies for determining comparability between agents. Large clinical outcome studies are indispensable for determining the safety and efficacy of a new and untested agent. However, they are often poor tools for use in comparing differences between two different agents unless the studies are made to include 1000s of patients - which may or may not reveal the difference in the product, In fact, I can think of only one example where the FDA required a large clinical outcome study for a product - yet the FDA first deemed the product not comparable due to analytic and pharmacokinetic and pharmacodynamic measures.

Rather, of all the hundreds of other brand biologic examples where comparability determinations were made, the analytic tests used to assess the molecular structure, chemical and biological function of the product, plus small pharmacokinetic and/or pharmacodynamic studies, were adequate for the FDA to provide a thumbs-up or thumbs-down to whether the new products resulting from changes in brand manufacturing processes were comparable or not.
In sum, the FDA scientists and physicians routinely make comparability determinations since manufacturing changes occur throughout the brand biologic product development and life-cycle. The comparability algorithm has existed for over a decade to allow brand biologic manufacturers to change and improve their manufacturing processes. Collecting data and learning from that data are at the core of this algorithm. With the ongoing development of ever more sophisticated and sensitive scientific tests, and with the FDA's ever-expanding knowledge of the safety and efficacy of biopharmaceutical agents, it is abundantly clear that the tools are available today to ensure the comparability and ultimate safety and efficacy of biogenerics.

As such, I believe, that based on the wealth of experience with brand postapproval manufacturing changes in the biopharmaceutical industry, the evidence clearly demonstrates that comparability processes soundly support the approval of biogenerics without the need for large and questionable clinical trials which for most products, would needlessly delay access to affordable life-saving medicines.

b. Immunogenicity

Immunogenicity, or the development of antibody and/or cellular immunologic reactions to biopharmaceutical agents, is a concern raised by others that I would like to briefly touch upon. Immunogenicity per se should not be used as an obstacle to establishing an abbreviated pathway for affordable biopharmaceuticals. Many biopharmaceuticals currently on the market have some level of immunogenicity and induce antibodies in some patients. But it is very unusual for these antibodies to cause a safety problem. The reality is that the generation of antibodies in reaction to a biopharmaceutical that does not affect safety or efficacy is inconsequential to the overall clinical status of almost all patients. Importantly, the FDA will have significant data based on the marketing history with the brand product before the time a biopharmaceutical is ready to be developed as a generic product. From this and the underlying product information, the FDA will have a greater sense of whether the product is immunogenic and if it is, whether the immunogenicity is related to any safety issues. Moreover, just like with brand products and post-approval brand product changes, the FDA will require the biogeneric product to assess aggregation and undergo a battery of tests and assays to demonstrate extensive analytical characterization in comparison with the brand product. Aggregation is one of the key analytical tests to assess for potential immunogenicity.
The proposed bill would allow FDA the flexibility to adequately assess all safety concerns, including immunogenicity concerns and may request clinical data when it deems it is necessary.

The safety of all biopharmaceuticals, including biogenerics, is a never-ending process. Ongoing post-marketing safety studies have and may be useful for assessing brand safety issues, including immunogenicity. The FDA can and should also use their authority under the bill to monitor the safety of biogenerics when necessary.. The need for such studies, or the type of studies that should be conducted, like for other scientific issues, is something the FDA should determine on a case-by-case basis. As a physician, there should be no cutting of corners on the safety of any agent.

It is important to note that at the House hearing in March, members heard that both brand and generic biologic products share the same concern of immunogenicity and that FDA has the ability to assess that risk. While immunogenicity is an important consideration for both brands and biogenerics, it is not an obstacle to their development.

c. Interchangeability Critical to Addressing Costs

I'd like to close with a brief discussion on "interchangeability." The term is used to denote when the FDA believes that physicians and other healthcare providers should have the flexibility and assurance that they may substitute biogenerics for the brand counter parts in the treatment of their patients.

The appropriateness of equating brand and biogenerics as "interchangeable" is a function of the adequacy of the science that exists for comparing these agents. I can say, without hesitation, that adequate scientific tools currently exist to assess and deem certain products as interchangeable. When all necessary and appropriate analytic data are comparable for products, and when these products have the same safety and efficacy profile at the same doses with comparable potencies, and when the FDA is satisfied that the database for these parameters is sufficiently robust to allow determination that substituting one product for the other will yield the same safety and efficacy profile of that of the brand biologic drug product — then the criteria for interchangeability will have been met.
It is interesting to note that the Agency has made clinically relevant agency product decisions.

For instance, the FDA approved GlaxoSmithKline's yeast derived hepatitis B vaccine and, in so doing, stated that the product is interchangeable to other hepatitis B vaccines derived from yeast and blood products. Yet, the example is instructive of how the Agency viewed "clinical interchangeability" for vaccines. These two agents were not identical products, and did not therefore have identical analytic properties. Nevertheless, the Agency recognized that these agents could be therapeutically used in the clinic interchangeably, i.e., as providing the same clinical effects. Likewise, the FDA also has previously recognized that some biogenerics products (menotropins injection and calcitonin salmon injection, desmopressin) are therapeutically interchangeable with their brand counterparts.[1]

Of course with biogenerics, the standards for interchangeability would be set by the FDA, and involve rigorous assessments of data from multiple parameters so that physicians could use either product knowing that the drugs would yield the same therapeutic and safety profiles.

Given the need for affordable, safe and effective biopharmaceuticals in the marketplace, and the adequacy of the science to determine, at least for some products, their interchangeability, as a physician I think it's very important that FDA be given legislative authority to use scientific data and make critical judgments to determine, when appropriate, that two products are interchangeable.

III. Recently Released FDA White Paper

As the Committee knows, the FDA released its long-awaited White Paper providing an historical perspective on the regulation of various types of follow-on and second generation protein products. The White Paper was significant on a number of fronts, not the least being that it confirmed that the FDA is currently evaluating biopharmaceuticals on a case-by-case basis and using an abbreviated process to review changes made to biopharmaceuticals. And all of this is done under the priority standard of ensuring safety and efficacy.

In the White Paper, FDA summarizes their long experience in considering scientific issues in the area of comparative analysis of proteins, issues that are central to a meaningful discussion of follow-on biologics. FDA reviewers have used their considerable experience and expertise through the years to formulate scientifically and data-driven approaches to addressing challenges presented in this area.

There are a number of important points that FDA made in the paper that must be stressed:

1. "scientific and technological advances have created new opportunities for the characterization and evaluation of protein products."
2. FDA has a long history of considering and addressing various scientific issues in this area
3. FDA has addressed the scientific challenges presented in this area using a case-by-case approach.
4. Some of the factors relevant to determining the comparability of protein products produced before and after a change in a specific manufacturer's manufacturing process are relevant to determining comparability between protein products produced by different manufacturers.
5. FDA does not always demand large clinical studies for post approval product changes.
6. FDA considers a number of factors when making determinations of comparability in this area, including the degree to which structural similarity between products can be adequately addressed, the extent to which mechanism of action is understood, the existence to which valid pharmacodynamic and pharmacokinetic assays, etc. are available.

In sum, it is clear that the FDA needs to be given both the regulatory authority and a wide scientific latitude to enable biogenerics to develop safely, efficiently and effectively.

IV. Summary

In closing, let me state that the science of comparability is not a new one. A deliberative process currently exists at the FDA to determine comparability today. This process is data-driven and heuristic: one builds upon what one has learned. Multiple analytic tools are used as a basis for establishing comparability. When needed and appropriate, data from additional pharmacokinetic and pharmacodynamic measures also could be required. In rare instances, it may be necessary for sponsors to conduct full clinical outcome studies to establish comparability.

The Access to Life-Saving Medicines Act proposes implementation of much of the same scientific processes and procedures that exist for the brand biologic industry when postapproval manufacturing product changes are made. Given the commonality of manufacturing changes by current manufacturers of biologic

agents, and given FDA's long and vast experience in assessing data from comparability studies, there is a wealth of resources available to draw conclusions on the safety and efficacy of comparable products manufactured by different manufacturing techniques.

The legislation gives FDA the authority and flexibility it needs to ensure safety and efficacy of biogenerics. It adopts the same scientific principles, processes and procedures that exist for the brand biologic industry when making post-approval manufacturing product changes to the biogeneric sector.

Why do I emphasize this? Because there have been discussions about changing the pathway and taking away some of the authority and flexibility the FDA needs to ensure that sound science drives the process. As a physician, a scientist and a former FDA official I must firmly state PROCEED WITH CAUTION when redefining a pathway. A truly workable pathway for biogenerics is one that brings safe and effective biogenerics to patients in a TIMELY manner. A pathway filled with needless requirements and hurdles will not accomplish what Congress wants – providing patients with the safe and affordable life-saving medicines they need.

My mission as a physician reviewer at the FDA, and that of all my colleagues then and now, was to protect the public by ensuring the safety of the supply of biopharmaceuticals for therapeutic use. No one's interests are served if safety is not viewed in this debate as paramount. It is clear to me that the science exists for FDA to ensure the safety of biogenerics using a workable pathway that reviews biogenerics on a case-by-case basis.

[1] See FDA's Ltr. to Congressman Stupak (Feb. 20, 2007) regarding protein products previously approved by the Agency under the Federal Food, Drug and Cosmetic Act (FDCA) at 3 along with FDA's Orange Book.

Mr. PALLONE. Thank you. Dr. Schenkein.

STATEMENT OF DAVID SCHENKEIN, M.D., VICE PRESIDENT, CLINICAL HEMATOLOGY/ONCOLOGY, GENENTECH, INC.

Dr. SCHENKEIN. Good afternoon, Mr. Chairman, and members of the committee. My name is Dr. David Schenkein, and I am vice president of Clinical Hematology and Oncology of Genentech. I have been a practicing oncologist for the past 20 years, and I am pleased to come before you today on behalf of the Biotechnology Industry Organization.

Genentech is considered the founder of the biotechnology industry. We began 31 years ago with the goal of developing a new generation of therapeutics created from genetically engineered copies of naturally occurring molecules important in health and disease. Our mission is to end the death sentence that cancer currently represents by creating medicines that will transform cancer into either a curable illness or a chronic condition.

In order to ensure that innovative biotechnology products continue to reach patients and physicians, it is essential that Congress adopt six key principles in creating any regulatory pathway for follow-on biologics. First and foremost, legislation must ensure patient safety. Patients should not have to accept greater risks or uncertainties in using a follow-on product and an innovator's product. In addition, legislation must recognize that biologics are far more complex than small-molecule chemical drugs. It must maintain the physician-patient relationship and allow only treating physicians to determine whether a follow-on product is interchangeable for the innovator product. It must preserve incentives for innovation, must ensure a transparent regulatory process, and must continue to prioritize the FDA's review of new therapies and cures.

In oncology we treat life-threatening illnesses. For many patients the first therapy is the chance for a cure that evaporates if the disease recurs, making it incurable. It is a critical window of opportunity. Take for example the situation that women with Her2 positive breast cancer face every day. At diagnosis, women are treated with a balance of chemotherapy and biologic Herceptin, along with surgery and radiation. For the majority of these women, in part because of the effectiveness of Herceptin, their cancer will not return. Imagine a situation where a woman is treated with a follow-on biologic in this setting that has even a slightly different profile which allows her cancer to return years later. The disease has now spread and her chances of survival are reduced significantly. What do we tell that woman and her family, that we never tested that follow-on biologic in humans but we thought it was similar enough to Herceptin and relied on those data to support its approval and to advocate for its use?

I firmly believe there will always be a need for clinical testing of a follow-on biologic. The amount and type of testing will depend on the specifics of the product and assessment of potential risks, and those determinations should be left to the FDA. Clinical trials will always be important to address questions such as immunogenicity. I would never take a biologic that had not been tested in humans. The risks are too high. New legislation should not court the others who may be less informed to do so.

In addition to scientific considerations, I would also like to address the importance of incentives. As an oncologist, I am extremely concerned about the potential that limited or no data exclusivity would have on agavent or early stage cancer drug development. It is in this setting that we hope to translate breakthrough discoveries into cures. Insufficient data exclusivity could strangle the incentives to continue investing in trials beyond the advanced or metastatic setting. Agavent studies are typically started only after positive phase three trials in metastatic cancer and are after-return data late in the patent life of the product. Trials of agavent therapy are intended to catch the cancer at the time before it spreads where our therapies could have the greatest impact for patients.

The approval for Herceptin in the agavent setting occurred 8 years after the original approval in the metastatic setting and involved more than 3,500 women in multiple randomized clinical trials. These trials can take easily more than 5 years from inception to completion at huge cost without any assurance of clinical success. Herceptin in the agavent setting reduced the risk of cancer occurrence by 50 percent, and if the cancer doesn't recur, these women cannot die from it.

This is our mission, to beat cancer through science, but without a substantial period of data exclusivity, it would be difficult for Genentech and others to invest in this critical but costly research. I am excited every day when I look at the pipeline we have at Genentech. We are developing biologics that starve tumors, cause cancer cells to self-destruct, and program them to behave differently in the body. It is my hope and that of BIO and Genentech that a transparent public process that leverages known scientific considerations will provide a framework and pathway for the approval of follow-on biologics. The stakes are simply too high to risk patient safety and potential cures by moving too quickly and not following the science.

Again, I thank you for the opportunity to testify before you today and look forward to answering any questions you may have.

[The prepared statement of Dr. Schenkein follows:]

STATEMENT OF DAVID SCHENKEIN, M.D.

Good morning, Mr. Chairman and Members of the Committee. My name is Dr. David Schenkein and I am vice president of Clinical Hematology and Oncology at Genentech, a leading biotech company headquartered in South San Francisco, California. I am pleased to come before you today on behalf of the Biotechnology Industry Organization (BIO) to offer my perspective on the issues relevant to any proposed framework for the abbreviated approval of follow-on biologics.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of health care, agricultural, industrial and environmental biotechnology products.

I hope you will find my contribution to this discussion constructive and useful as you seek out a sound, science-based path forward for follow-on biologics while preserving patient safety and incentives for biomedical innovation.

By way of introduction, I have been a medical oncologist and hematologist for over 20 years. I have spent most of my career caring for patients with life threatening illnesses. It's been my job to sit with patients and their families and make decisions on the most appropriate therapy to choose—- many times a choice of risk benefit that has life and death implications. Prior to joining Genentech, I spent 17 years in academic and clinical medicine as an attending physician in Hematology Oncol-

ogy at the Tufts-New England Medical Center in Boston, where I was an associate professor and held the position of director of the Cancer Center. I will soon be on the oncology faculty at the Stanford Cancer Center.

I previously served as the senior vice president of Clinical Research at Millennium Pharmaceuticals in Cambridge, where I oversaw the clinical development of Velcade, a first-in class cancer therapy now approved to treat multiple myeloma and non-Hodgkins lymphoma. In my current role at Genentech, I am responsible for leading the medical and scientific strategies for our BioOncology portfolio, including overseeing the development of a robust pipeline of novel cancer therapies and marketed products, including Avastin, Herceptin, Rituxan and Tarceva.

My company, Genentech, is considered the founder of the biotechnology industry. Genentech was founded 31 years ago with the goal of developing a new generation of therapeutics created from genetically engineered copies of naturally occurring molecules important in human health and disease. Within a few short years, Genentech scientists proved it was possible to make medicines by splicing genes into fast-growing bacteria that produced therapeutic proteins.

Today, Genentech continues to use genetic engineering techniques and advanced technologies to develop medicines that address significant unmet needs. Genentech is among the world's leading biotechnology companies, with 14 products on the market for serious or life-threatening medical conditions, over 50 projects in the pipeline and more than 10,000 employees.

The researchers and clinicians at Genentech are working to fundamentally change the way cancer is treated by developing a broad portfolio of innovative targeted therapies designed to improve and extend the lives of cancer patients. Put simply, we are trying to end the death sentence that cancer currently represents by creating medicines that will transform cancer into either a curable illness or a chronic condition. We strive for the time when a diagnosis of cancer leads to a discussion similar to the one that occurs today around high blood pressure or diabetes.

I would like to begin by noting that I appreciate the concern Congress has shown for patient access to biologic therapies. It is a concern that I share—as does Genentech, and as does BIO. While legislation on follow-on biologics has the potential to increase access to some medicines, that legislation must be well-founded in science and ensure that the medicines to which access is provided are no less effective or safe than medicines already on the market. I believe that through the proper process, those critical goals can be met.

In order to ensure that new pioneer biotechnology products continue to reach patients and physicians, it is essential that Congress adopt six key principles as it explores the creation of any regulatory pathway for follow-on biologics. I will touch on these principles in my testimony, but will focus principally on the first three since my expertise is as a physician and a scientist.

- Ensure Patient Safety. Patients should not have to accept greater risks or uncertainties in using a follow-on product than an innovator's product.
- Recognize Scientific Differences Between Drugs and Biologics. Biologics are much more complex than small molecule chemical drugs.
- Maintain the Physician-Patient Relationship. The current state of science is not sufficient to establish interchangeability for complex follow-on biologics. Accordingly, Congress should ensure that patients are not given follow-on biologics unless expressly prescribed by a physician.
- Preserve Incentives for Innovation. Any statutory pathway for follow-on biologics must include a substantial data exclusivity period; must respect our intellectual property rights; and must provide adequate notice and process rights.
- Ensure Transparent Regulatory Processes. Any legislation must require FDA to follow a transparent and public process in determining data requirements for the approval of specific follow-on biologics.
- Continue to Prioritize FDA Review and Approval of New Therapies and Cures. Congress must ensure that workload associated with follow-on applications does not harm the FDA's ability to efficiently review new drugs and biologics.

First and foremost, patient safety must be assured. I trust that patient safety is a concern that we all share and that it will be a guiding concern for Congress as you consider a statutory pathway for follow-on biologics.

If follow-on biologics are to achieve the same standards of safety and efficacy as pioneer biotechnology products, then clinical trial evidence and data must be a fundamental requirement, and must be conducted on a product-by-product basis. The safety and effectiveness of a follow-on biologic simply cannot be assured without clinical testing, and in particular, immunogenicity testing, which is necessary to avoid putting patients at risk of adverse effects from immune reactions.

The stakes are too high to take the risk of moving too quickly and not following the science. In oncology, like in other therapeutic areas, we make our decisions on therapy selection based on clinical data and a deep understanding of both safety and efficacy: the risk to benefit ratio. Somewhat unique to oncology is the life-threatening nature of the illnesses we treat and the consequences of a wrong choice. For many patients, the first therapy is a chance for a cure that evaporates if the disease recurs, making it incurable.

Take for example the situation that women with Her2 positive breast cancer face every day. At diagnosis, women are treated with a balance of chemotherapy, including the biologic Herceptin, directed at the cancer protein along with surgery and radiation. For the majority of these women, their cancer will not return. Imagine a situation where a woman is treated with a follow-on biologic in this setting that has even a slightly different risk-to-benefit ratio, which allows her cancer to return years later. The disease has now spread and her chances of survival are reduced significantly. What do we tell that woman and her family? That we never tested that follow-on biologic in humans, but we thought it was similar enough to Herceptin and relied on Herceptin's data to support its approval and to advocate for its use?

To understand why we should always expect some need for pre-market clinical testing and immunogenicity testing of follow-on biologics, it is important to understand the nature of biologics in general and how they differ from small molecule therapies.

Differences Between Biologics and Drugs

With small molecule drugs—for example, the conventional pills you see on pharmacy shelves and in medicine cabinets—you are working with substances that are relatively small, relatively simple in structure, and relatively easy to replicate using carefully controlled processes. Most importantly, their relatively small size and simple structure allow precise characterization and detection of even minor changes in the product.

Biologics are vastly different from small molecules in all these aspects. In contrast to small molecules, biologics are very large—typically several hundred- or thousand-fold larger. They are produced not by well-controlled chemical processes but by complex living cells and organisms through extremely complicated and sensitive manufacturing processes.

As innovator companies' experience with respect to pioneer biotechnology products has shown, and as FDA has long emphasized through its regulation and guidance, small product or manufacturing differences in biologics can result in significant safety and/or effectiveness differences. To a far greater extent than small molecules, biologics frequently can bind to themselves to form pairs or aggregates, can change their shape over time or with minor changes in conditions, and can interact with materials in their containers and packaging. They are relatively unstable and are sensitive to how they are handled, processed and stored as they have the ability to assume many forms and variants. They are typically not homogeneous in chemical structure; rather, they are a large family of molecules with related, but not identical, structures. They cannot be fully characterized, so not only are differences common, they can be extremely difficult to detect, and their effects on the product's safety and efficacy are extremely difficult to predict.

As a result, the regulation of biologics is largely based upon strict control of the manufacturing process to minimize the likelihood of changes to safety and efficacy. Additional clinical testing is often required when substantial changes to the manufacturing process occur, and certainly the type of changes and differences in manufacturing necessary to producing a follow-on product would meet such a threshold.

While the ability to characterize biological products using physical, chemical, and biological testing has improved as science has advanced, current laboratory testing—without testing in patients—is still very far from sufficient to ensure that a follow-on biologic is without differences from a reference product. These differences could adversely affect its safety or efficacy.

Furthermore, the methods used by innovators to demonstrate continued safety and effectiveness after a manufacturing process change are insufficient to demonstrate safety and effectiveness of a follow-on biologic made by a different manufacturer using a different process. When a biologics manufacturer makes a substantial change to its process (e.g., new cell line), given the incomplete ability of laboratory testing to identify or predict differences, FDA requires substantial testing in humans (clinical testing) to validate the comparability of the product. And clinical testing often reveals differences. This is important because by definition, the manufacture of a follow-on will necessarily involve very substantial manufacturing

changes—a new cell line, a new facility, and a new process. These changes will result in a different product, and vastly increase the likelihood of clinically important differences, which can only be understood through clinical testing in humans.

The manufacturer of a new follow-on biologic also faces several limitations in its ability to identify clinically important differences short of clinical testing. When a manufacturer makes substantial changes in its manufacturing process, that manufacturer is able to compare not only the final product but also various components and intermediates that are produced during various stages of the new and old manufacturing process. For example, depending on the changes made, comparisons might be made of the unpurified biologic (made by the old and new processes), and/or of purified product prior to formulation. Such comparisons may detect important differences that remain in the final product, but at levels that make them undetectable in the final product. Manufacturers of follow-on biologics will not have these materials for testing and will only have access to the final, marketed reference product.

Additionally, optimal comparisons of "before change" and "after change" materials require an understanding of which parameters are key to ensuring the safety and efficacy of the molecule and what the best approaches are to assessing them. This understanding comes from years of working with the reference product, which is not available to manufacturers of follow-on biologics. Further, when differences are detected, the key question becomes whether the difference is clinically important. While manufacturers of innovator products have extensive experience that sometimes helps address this question, the manufacturer of a new follow-on biologic will have limited experience with the molecule.

Thus, the ability of an innovator to make changes to its own manufacturing process, subject to the FDA's comparability guidelines, is simply not analogous to a follow-on company proving "comparability" when entirely different manufacturing processes are used. A manufacturer of a follow-on biologic will face significantly more limitations in demonstrating "comparability" than a manufacturer modifying its own process. When we make changes that might affect the clinical effects of a product, we also face an appropriate requirement for clinical studies to ensure safety and efficacy. How can we accept a lesser standard of evidence from the manufacturers of follow-on biologics who face even greater limitations in laboratory testing, without significant concerns for safety?

Clinical trial evidence and data are fundamental for evaluating and demonstrating the safety and effectiveness of a follow-on biologic

In light of the limitations described above, and based on my experience, I firmly believe that there will always be a need for clinical testing of a follow-on biologic to provide adequate assessment of potential changes. The amount and type of testing will depend on the specifics of the products and assessment of potential risks, and those determinations should be left to the FDA. Clinical trials will always be important to address questions such as immunogenicity, pharmacokinetics, and common adverse events under controlled conditions before a product is marketed. I would never take a biologic that had not been tested in humans; the risks are too high. New legislation should not cause others, who may be less informed, to do so. Congress should not create two standards for these products—those appropriately tested for safety and efficacy and those that are not.

There are many examples of how seemingly minor changes in a biologic's manufacturing process have resulted in significant changes in the product—changes that could only be detected through clinical testing. I would like to use some specific examples to ensure that this Committee's members understand that my concerns are not theoretical or alarmist in nature, but are in fact very real issues that need to be considered.

In our case, Genentech was working with a business partner, Xoma, to develop a product for psoriasis. When it came time to transfer the technology from Xoma's facility to our own state-of-the-art manufacturing plant, we were unable to produce material that met the pre-defined statistical definition for comparability. During Phase III testing, minor manufacturing modifications were made to allow for large-scale material production. The pharmacokinetic (PK) studies we conducted suggested that the Genentech material achieved a slightly higher serum concentration than the Xoma material. Because we could not be sure that the product we produced at Genentech, which was different than that produced at Xoma, was safe, we agreed to do additional clinical testing. Fortunately, Genentech was able to prove to the FDA that the new material was safe, but FDA approval of the product was delayed by more than a year.

While this is a good example of a manufacturing change resulting in differences that, once re-tested, proved to be acceptable, there are plenty of examples where seemingly minor differences have had catastrophic consequences. Irrespective, we

agreed with the FDA's decision that we must re-test our product to ensure its safety and effectiveness.

IMMUNOGENICITY TESTING IS NECESSARY TO AVOID PUTTING PATIENTS AT RISK OF ADVERSE EFFECTS FROM IMMUNE REACTIONS

Special attention should be given to the problem of immunogenicity: the ability of most or all biologic products to stimulate an immune system response in the body, prompting the formation of antibodies. Immunogenicity is particularly important in the context of manufacturing changes for biologics because (I) product differences that are difficult or impossible to detect can lead to changes in immunogenicity; (2) changes in immunogenicity can impact on safety and efficacy in many ways and (3) immunogenicity can be assessed only through clinical testing. The immune system evolved to distinguish foreign proteins (e.g., bacteria, viruses, proteins from other people) from its own proteins as a means of survival. This means that our immune systems can be exquisitely sensitive to differences in proteins.

Thus, there is great potential for seemingly minor changes in therapeutic protein products, even those not detected by physical, chemical, and biological testing, to result in clinically significant changes in immunogenicity.

Most biologic products have some degree of immunogenicity; that is, they will cause formation of antibodies in some patients. For vaccines, this is desirable. For therapeutic proteins, these antibodies can inactivate the protein or cause it to be cleared from the body, resulting in a loss of efficacy and the progression of the disease. Patients with hairy cell leukemia treated with interferon alfa, for example, have been reported to experience a relapse of disease when antibodies develop. Similarly, some patients receiving insulin and blood clotting Factors VIII and IX have been reported to lose responsiveness after developing antibodies.

In addition to inactivating or clearing a drug, antibodies bound to a drug can also play a direct role in causing various adverse effects. Patients who have developed antibodies to experimental biologics have experienced consequences including joint swelling, fever, and encephalitis. Even for approved biologics, it is not uncommon that the development of antibodies during treatment increases the likelihood of having adverse reactions, sometimes even severe, at the site of subsequent injections or following subsequent infusion into the blood stream.

In addition to these effects, and more serious still, antibodies can also inactivate the body's naturally occurring protein, resulting in adverse and even life- threatening side effects. Patients who received an experimental biologic version of thrombopoietin, a protein that stimulates production of platelets critical for blood clotting, developed antibodies which neutralized not only the biologic, but also their own naturally produced thrombopoietin, resulting in problems with bleeding.

The case of EPREX, a biologic product sold in Europe by Johnson & Johnson companies, illustrates how even a seemingly minor change can increase a product's immunogenicity and cause harm to patients. In 1998, J&J changed the stabilizer in its EPREX formulation at the request of European authorities because of concern in Europe that the human serum albumin stabilizer could theoretically transmit Mad Cow Disease. The switch from the old stabilizer to another well-established one seemed simple enough and relatively benign. Indeed, it was intended to improve the safety profile. It was applied to a variety of product presentations, including single-use vials and pre-filled syringes with both Teflon-coated and uncoated rubber stoppers.

However, shortly after this seemingly minor change, there was an increase in the incidence of antibody-mediated pure red cell aplasia (PRCA) among patients taking EPREX. Pure red cell aplasia is a serious condition in which the bone marrow ceases to produce red blood cells. Patients suffering this adverse event must undergo blood transfusions weekly for the remainder of their life. It took four years of extensive investigations involving more than 100 experts from clinical, pre-clinical, manufacturing, process sciences, logistics, quality, analytical, and regulatory fields and in excess of one hundred million dollars to identify the cause. The conclusion was that uncoated rubber stoppers, when exposed to the new stabilizer, released substances called leachates into the EPREX formulation and that these substances were most likely responsible for the increase in the product's immunogenicity and the resulting increase in patients developing pure red cell aplasia.

It's important to note that the examples I have given are just some of the cases in which immunogenicity concerns have arisen. Most biologics have some degree of immunogenicity. Immunogenicity levels can change with even slight changes in their manufacturing process and can have clinically important consequences. Scientifically, the only way to detect immunogenicity is through clinical testing.

In summary, extensive experience confirms that manufacturing differences, such as those between the processes of an innovator and follow-on, are likely to lead to differences in product safety or efficacy, which will be detected best or only through clinical testing. That is not to say that a full clinical testing program must be required for follow- on biologic products. Abbreviated clinical testing will sufficiently address key areas of uncertainty regarding safety and efficacy on a product-by-product basis, particularly where there exist good measures of desired effects (so called pharmacodynamic measures) and where a high degree of similarity is demonstrable. But experience has made clear that clinical studies must be considered a necessary and mandatory part of properly evaluating any and all biologic products, and must be a fundamental foundation upon which any proposed regulatory pathway for the approval of follow-on biologics is created.

In addition, we believe that a follow-on product should be approved only for conditions for which the reference product is approved. For all the reasons discussed earlier, the safety, purity, and potency of the follow-on product for each indication must be supported independently, and attention must be paid to special safety risks (including possible immunogenicity) in different patient populations.

Interchangeability and substitutability: Congress should ensure that patients are not given follow-on biologics unless expressly prescribed by a physician

Given the complexity of biologics, the high potential for process differences to result in clinically meaningful product differences, and the limited ability to detect differences between a follow-on and reference biologic, a determination of comparability for a follow-on product is particularly challenging. Ensuring comparability of a follow-on biologic to a reference biologic with an acceptable degree of assurance will be made much more challenging by the follow-on manufacturer's limited access to information about, and lack of experience with, the innovator's process as well as their lack of access to intermediate, in-process materials. As a result, we believe that establishing the interchangeability of different products is not feasible, and therefore, is a decision that is only appropriately made by a treating physician.

No amount of non-clinical testing of a biologic product can ensure or predict it will have identical effects to another product. Although clinical testing can place limitations on the possible extent of differences, for most products, only extensive comparison studies could rule out clinically significant differences. For example, if a reference biologic caused a serious or fatal effect in one patient in 1000, and a new drug had twice the risk, it would take a study of about 50,000 patients to have a good chance of detecting this important difference.

Given the risk of clinically important differences always at play and the possibility that substituting products would increase the risk of clinically important antigenicity, it is imprudent and potentially dangerous to allow the follow-on biologic to be considered "interchangeable" with its reference product.

The European Union (EU) rightly acknowledged in its own process of developing a pathway for follow-on biologics that follow-ons can be similar, but never identical to an innovator biologic. After very careful review of the data, the EU recognized the danger of applying "interchangeability" status to follow-ons, a misnomer that could lead physicians and patients to inappropriately assume sameness and substitute one for the other, with potentially serious adverse health consequences. Just a few months ago, the French Parliament adopted legislation to prevent follow-on biologics from being treated in the same way as traditional generics, and banned the automatic substitution of one biologic medicine for another.

Given the current paradigm allowing for the substitutability of generic drugs with the innovator products they copy, a determination of interchangeability in this context would likely encourage the substitution of one product for another. The FDA itself expressed concerns about substitution of one biologic medicine for another in a statement last September: "Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response" *(http://www.fda.gov/cder/news/biosimilars.html,* September 2006). Even if products have a determination of comparability but not interchangeability, substitution could occur, potentially unbeknownst to the prescribing physician or patient and potentially with adverse health outcomes.

In addition, it will be important for Congress to ensure that follow-on biologics are assigned a unique name—one that has not be adopted for any protein manufactured by a different person—so that it is readily distinguishable from that of the innovator's version of the product. Assigning the same name to a product that is not the same would be confusing and misleading to patients, physicians, and pharmacists, could result in inadvertent substitution of the products, and would make it difficult to quickly trace and address adverse events that may be attributable to either the innovator or follow-on product.

Furthermore, if aspects of a follow-on biologic's approach, such as the designation of interchangeability, led to substantial numbers of patients switching between therapies, it could severely impair the ability of pharmacovigilance systems to deal with emerging safety problems. When a new adverse event emerges or a known one increases in frequency, it may be impossible to attribute the adverse event to a specific product if patients experiencing the event have received multiple products. This is especially the case for some types of adverse events, such as those due to immunogenicity, that tend to arise in patients well after receiving the causative product. Should a particular follow-on biologic be associated with such a safety problem, the impact of being unable to determine which "interchangeable" biologic was responsible could be devastating. The ability to detect that a new follow-on biologic has a significantly higher risk would be highly impaired and the difference in risk could go unnoticed. When new risks are noticed, it could well be impossible to determine to which "interchangeable" biologic it was attributable, and appropriate use of the entire group of therapies might be severely impaired because of a concern with one. Such a class effect is not in the best interest of patients or the industry generally, as overall confidence in biologics would be damaged.

Follow-on biologics should be properly evaluated through post-marketing surveillance and post-marketing clinical studies

All approved follow-on biologics will inevitably be associated with some risk that potential safety problems will become apparent only in the post-marketing period because (1) not all differences between a follow-on and reference product will be detectable in pre-market testing, (2) one cannot predict with certainty which differences may have adverse impacts on safety and efficacy, and (3) some risks may become apparent only after extensive use. To optimize patient safety and to control such risks, it is critical that the FDA not be limited in its ability to require post-marketing clinical studies when appropriate. Follow-on manufacturers should also be required to monitor a product for safety problems through a robust post-marketing safety surveillance program.

After all of the attention Congress has given to the issue of drug safety evaluation, it would be intellectually inconsistent for this Committee to pass legislation that does not put forth specific provisions enabling adequate regulatory requirements for post-marketing safety surveillance programs and clinical studies of follow-on biologics. It would be equally problematic for any follow-on legislation to limit the ability of expert reviewers to negotiate for post-marketing clinical studies that could protect public safety.

Since it is not possible to make two biologic products identical, follow-on biologics policy will, by definition, allow abbreviated applications for molecules that are highly similar to a reference, despite known or potential differences. However, a follow-on product must be as similar to the reference product on which it relies as can be achieved, in view of current scientific knowledge and technological capabilities. It must have the same route of administration, dosage form, and strength as the reference product.

In addition, one must draw a line as to how much of a difference should be allowed as there is no scientific basis for allowing abbreviated testing of a new biologic on the basis of it being only distantly related to an existing one. Some differences are so substantial that the biologics should be considered different products entirely.

Differences in Amino Acid Sequence

The amino acid sequence defines a protein. Even a minor difference creates a different (mutant) protein, and a product containing a mutant protein is a different product from the non-mutant form. Given the potential for such a product to have different effects, any such product should be subject to all the standard safety and efficacy testing to which you would subject any innovator drug.

Differences in even just one amino acid can have devastating effects on the function of a protein. Single amino acid mutations in a person can be lethal or result in serious diseases such as sickle cell anemia and cystic fibrosis. Single amino acid mutations in a virus can change it from benign to deadly or from treatable to resistant to treatment. And single amino acid changes in therapeutic biologics, sometimes made in an attempt to improve potency, durability or other desirable traits, often have adverse effects on the molecule, with the potential to pose great danger to patients.

The AspB 10 insulin analogue is a prime example. This was a biological product that had only one amino acid difference from the insulin amino acid sequence. At the time it was being studied, it seemed reasonable to think that this insulin analogue would be safe. However, to the great surprise and concern of all involved,

when AspB 10 was given to laboratory rats, it triggered the development of breast cancers.

When a change in an amino acid has occurred during premarket development, FDA has required extensive testing of the new molecule rather than assuming the properties of the former molecule were retained. To allow marketing of new mutant protein therapeutics with anything short of the testing required of any new protein therapeutic potentially exposes patients to very real risks.

As noted above, the need to tolerate some differences in a follow-on biologic from its reference product arises from technical limitations on the inability to exclude, or in some cases to identify some differences. But there is no technical limitation preventing a manufacturer of a follow-on biologic from producing one with an amino acid sequence identical to that of a reference.

Differences in Post-Translational Events

"Post-translational modification" refers to the important processes that occur after the backbone of a protein has been synthesized. It can result in major chemical modifications of the protein, such as attaching additional chemicals, modifying the chemical structure, cross-linking, and removing large parts of the protein. Post-translational modifications can, and often do, have a major impact on the activity, half-life in circulation, and immunogenicity of a protein. Many types of post-translational modifications leave no scientific basis for a determination of comparability and submission of abbreviated applications.

Any difference in post-translational modification will require significant clinical testing to determine what difference it makes clinically. But many are so profound, they should simply be considered to make the biologic a different biologic, requiring a full application.

Preserve incentives for innovation

In order to preserve incentives to research, develop and manufacture new innovative therapies and cures, as well as new indications for such products, any statutory pathway for follow-on biologics must also provide a substantial period of data exclusivity; must respect intellectual property and other legal rights; must provide adequate notice and process rights; must ensure a transparent statutory and regulatory process; and must continue to prioritize the review and approval of new therapies and cures. The importance of these measures is explained below.

Include substantial non-patent data exclusivity, during which time follow-on manufacturers could not rely on the FDA's prior approval of pioneer biologics to support approval of their own products. Such data exclusivity is necessary because a follow-on biologic may be similar enough to a pioneer biologic for regulatory approval purposes, but different enough to avoid infringing the innovator's patents. Thus, non-patent exclusivity is necessary to maintain effective market protection. Further, the fledgling nature of the biologics industry, its heavy dependence on access to significant amounts of high-cost public and private investment capital, and the high risks and costs involved in the development of new biologic medicines all warrant a substantial period of exclusivity.

Respect intellectual property and other legal rights. Follow-on biologic products should not be approved until after all statutory protections, including data exclusivity and patent protections, are no longer available for the approved pioneer product. Any follow-on biologics pathway should fully respect existing protections for trade secret and confidential commercial information, and not permit the use of such protected data for the purpose of approving follow on products. It also must not abrogate or limit constitutional or statutory rights of patent holders to protect against infringement.

Provide adequate notice and process rights. Any follow-on biologics regulatory pathway should ensure that patent challenges are litigated or otherwise resolved prior to marketing approval of the follow-on product, in order to protect the innovator's intellectual property rights and avoid confusion in the medical, patient, and payer communities. Further, any follow-on biologics regulatory pathway should not create special patent litigation rules that favor follow-on biologics manufacturers.

Ensure transparent statutory and regulatory processes. Manufacturers of innovator products should be provided full and fair opportunities to engage Congress and other stakeholders in a meaningful public process. Establishing a balanced and rigorous statutory pathway for follow-on biologics requires deliberative evaluation of numerous complex scientific, legal, intellectual property and economic issues. Further, any such pathway must require that FDA follow a transparent and public

process in determining data requirements for the approval of specific follow-on biologics.

Continue to prioritize FDA review and approval of new therapies and cures. Any applications for approval of follow-on biologics will raise novel and complex questions of science and law, requiring substantial time and additional resources to ensure a thorough regulatory review for safety, purity, and potency. In order to avoid slowing down the FDA's review and approval of new therapies and cures, many for currently untreatable and serious diseases, Congress must ensure that workload associated with these new applications does not harm the FDA's ability to efficiently review new drugs and biologics, and that new treatments continue to have the highest review priority.

As an oncologist and leader of a comprehensive oncology clinical development program, I am extremely concerned about the potential that limited or no data exclusivity would have on adjuvant—or early-stage—cancer drug development. It is in the adjuvant setting that we hope to translate the breakthrough discoveries into cures for many of the incurable cancers that face us all. Limited data exclusivity in a follow-on biologics bill will lessen or eliminate the incentive successful cancer innovators have to continue investing in trials beyond the metastatic—or advanced stage - disease setting, since successful adjuvant trials are apt to return data suitable for an FDA submission late in the patent life of the product.

This is a significant issue because it could hinder research and development in the adjuvant setting. These studies are typically started only after positive Phase III trials in metastatic cancer and could take too long to be valuable and allow us to re-invest further in developing innovative therapies. Trials of adjuvant therapy are intended to catch the cancer at the time before it spreads, where our therapies could have the greatest impact for patients. Therefore, the need for randomized controlled trials is at its strongest in the adjuvant setting and requires a significant investment of time, money and human resources, as these trials are much larger in size. I will provide a couple of examples to help explain just how important this is to patients and our ability to potentially end the death sentence that cancer now represents.

In the case of our drug for HER2 positive breast cancer, Herceptin, we were only able to show that the drug could cut the recurrence of breast cancer in half in women with adjuvant HER2 positive disease years after completing a rigorous clinical trial and submission program in metastatic HER2 positive breast cancer. Prior to completing additional clinical studies of Herceptin, a diagnosis of HER2 positive breast cancer was among the most deadly a woman could receive. The approval for Herceptin in the adjuvant setting occurred 8 years after the original approval in the metastatic setting, and involved more than 3,500 women in multiple randomized clinical trials. These trials can take easily take more than 5 years from inception to completion at the cost of hundreds of million dollars each, without any assurance of clinical success.

The Herceptin adjuvant program marked a first step in a major initiative to conduct studies of Genentech's targeted therapies in earlier stages of disease. This is again a critical issue when I think about the potential Avastin may have to treat patients with early-stage cancer. There are currently more than 300 clinical trials of Avastin underway today in more than 20 tumor types—including ovarian, brain and adjuvant colon cancer. Our investment in the robust Avastin development program is based on what we learned about the safety and efficacy of Avastin in metastatic colon, lung and breast cancer trials over the past decade.

Avastin is designed to interfere with the blood supply to a tumor by inhibiting VEGF, a protein that plays a critical role in angiogenesis, the formation of new blood vessels to the tumor. Genentech scientists identified the gene for VEGF more than 15 years ago and despite approval to treat patients with metastatic colon and advanced non-small cell lung cancer in the past 3 years, we are still years away from fully understanding how Avastin can best help patients with early-stage disease in the critical time before their cancer spreads.

THE EU APPROACH TO BIOSIMILARS

We are fortunate that the EU has already made substantial progress in developing and implementing a policy based in good science and public health, and is consistent with their unique regulatory and health care framework. We should be able to leverage that work to have a frank and transparent scientific debate here in the United States, allowing us to develop a model which will be compatible with our own regulatory and health care system.

The key features of the EU process stem from the recognition of the unique characteristics of biotechnology derived proteins. Several years ago, EU legislation clear-

ly distinguished a "biosimilar" (the term they use for follow-on biologics) from a "generic" because of the manufacturing principles for biologics that are discussed above. The EU legislation did not attempt to define the scientific standards for approval of biosimilars. Instead, the EMEA, the science-based body responsible for approving the marketing of drugs in the EU, was trusted with that task. Furthermore, the EU legislation did not seek to constrain the ability of the EMEA to require data to ensure the safety and efficacy of biologics. The EU legislation clearly distinguished a "biosimilar" from a "generic" due to the many scientific concerns discussed above; the EU also recognized the inherent dangers of interchangeability.

The EMEA provided a broad regulatory framework, including the development of guidance documents, which outline the data requirements necessary to for the approval of these products. They pursued a science-based, transparent and open process to establish concept papers and draft guidances, starting first with basic principles for all biosimilars. This was followed by more specific guidances, which enumerate testing requirements on a product class-by- product class basis. This transparent process included public scientific workshops in which all parties were invited to offer input. The EU testing requirements do allow for abbreviations in testing where science and safety permit; however, clinical testing, immunogenicity testing, and post-marketing safety surveillance are all critical parts of those requirements. In fact, those requirements were deemed essential to minimize the risk to patients. The EU pathway strives to achieve follow-on biologics that are truly highly similar to a reference product while acknowledging that important clinical differences may still exist upon market approval, making post-marketing clinical studies and safety surveillance important.

In conclusion, I sincerely hope that the experiences and principles I have discussed have informed this debate. It is my hope that as you examine proposed legislative pathways for follow-on biologics, you will pursue a scientifically driven public debate to ensure that public policy is well- founded in science and supports the development of follow-on biologics that are safe and effective. We must ensure that we pay the appropriate attention to the principles of patient safety that are being discussed in this country and in these halls right now.

It is my hope, and that of BIO and Genentech, that a transparent public process leveraging known scientific considerations will provide a framework and pathway for the approval of follow-on biologics in the United States—a pathway that has an overriding concern for patient safety and well-being. It is also critical that such a framework appropriately provide incentives for innovation so that the promise of new and innovative biologic therapies will be realized for generations of patients to come.

Again, I thank you for the opportunity to submit testimony for this hearing, and look forward to answering any questions you may have.

Mr. PALLONE. Thank you. Dr. Allan.

STATEMENT OF GEOFFREY ALLAN, PH.D., PRESIDENT, CEO, CHAIRMAN OF THE BOARD, INSMED, INCORPORATED

Mr. ALLAN. Good afternoon, Chairman Pallone, and members of the Health Subcommittee. Thank you for the opportunity to testify today.

I am Geoffrey Allan, president, CEO, and chairman of the board for Insmed, Incorporated, a small biotechnology company whose goal is to provide therapeutic products for metabolic and endocrine disorders. I am here this afternoon, to urge Congress to pass legislation that defines a practical, science-driven approval pathway for biogenerics based on the key principles that timely approval and timely commercialization of biogenerics will create savings to publicly financed healthcare programs and will accelerate research and development of new and improved lifesaving medications.

As a pharmacologist, I have spent 27 years in drug research and development at both mature pharmaceutical companies and early-stage companies like Insmed. I entered this field because I understand complex molecules and I have dedicated my work at Insmed to helping patients with rare disorders. It is now my mission to uti-

lize the scientific experiences and capabilities of our industry to bring medicines to patients where there is an unmet medical need. My goal is to extend our mission to include working with the backbone of the biotech industry, the researchers, the contract manufacturers, and like-minded small research and development companies to unleash our scientific expertise for the development of biogeneric molecules.

In 2005 Insmed received FDA approval for a drug called IPLEX. This drug is an orphan drug to treat children with a rare growth disorder. It is a recombinant protein molecule and it is similar in complexity to many of the recombinant protein products that are the topic of discussion regarding biogenerics.

We believe our experience with the development and approval of IPLEX has positioned us to successfully manufacture biogenerics. We have developed the infrastructure for the manufacture, the preclinical and clinical evaluation for recombinant protein products, and we now want to leverage that expertise for the development of generic recombinant proteins. As I said, we have the scientific and technical experience, the personnel, and the facilities to produce safe and affordable generic biologics. I believe our experience with IPLEX is very illustrative of the scientific and technical issues that confront biogeneric drug developers, issues such as comparability testing, the nature of clinical data needed to support the characterization of a biogeneric product. Given our experience of the manufacturing and clinical development of IPLEX and including structurally characterizing proteins, ensuring potency and purity, I believe the scientific expertise and capability exists for many companies to manufacture safe and affordable biogeneric products.

In an effort to provide scientific insight into our experiences, Insmed implemented several manufacturing changes during the production of IPLEX. We changed cell lines, we changed locations, we changed overall facilities. We still maintained the purity, the consistency of the product. The impact of the manufacturing changes was assessed by comparability testing in which we used extensive analytical tests and short-term clinical studies to determine if any changes to the product resulted. Our experience with IPLEX gave us the expertise also in longer term clinical outcome studies and in the assessment of the immunogenicity which measures the potential antibodies to the IPLEX product.

One might ask how our expertise in the production of one recombinant protein product would allow us to develop any generic protein. Although the manufacture of each product is unique, they all share the same types of manufacturing processes, the same internal quality control systems are used to monitor these processes. The manufacturing procedures for different proteins have actually more in common than they are dissimilar. The same basic technologies and principles are applied to fermentation, expression, and purification of any recombinant protein product produced. We would not need information on the manufacturing methods used for the brand product but instead would use our own expertise and tailor it to the specific generic protein of interest.

In fact, some of the exact test methods or specifications set by the innovator company that were to standardize the brand product may well be outdated. Analytical technology has advanced consid-

erably over the last 20 years, and therefore there is a real possibility that generic protein drugs will have a more robust characterization than the innovator product.

Brand companies have been quick to point out that sometime things can go wrong during the manufacture of a recombinant protein product. That is true. I do not know of any industry where occasional errors do not happen. However, it is critical to understand that there are safeguards that prevent any potential errors from ever affecting the safety of the product. Patient safety is paramount, and I believe we enforce good manufacturing practices that manufacturers do follow, as well as the process and the testing, the evaluation that is conducted by the Food and Drug Administration in order to obtain approval, whether the product is brand or generic. There is no reason to believe that a generic biologic would be of a lesser quality and less safe than a brand product. The FDA has only one single standard to approve safe and effective products.

You have heard that the science now exists to allow for the safe production——

Mr. PALLONE. Doctor, if you can summarize, you are about a minute over.

Dr. SCHENKEIN. I apologize. The summary is essentially we know that the science is here, we would like to be involved in the development of these products, and I would like to thank you very much for the testimony this afternoon.

[The prepared statement of Mr. Allan follows:]

STATEMENT OF GEOFFREY ALLAN

Good morning Chairman Pallone, Chairman Dingell, Ranking Members Deal and Barton, and Members of the Health Subcommittee. Thank you for the opportunity to testify today.

I am Geoffrey Allan, president, CEO and chairman of the board of Insmed Incorporated. I testify before you this morning as Chairman of the Coalition for Biotechnology Innovation (CBI), and it gives me great pleasure to announce the launch of this newly formed organization to give a voice to small biotechnology companies that are being brought together by a shared interest in advancing innovation in the biotechnology industry. Our primary goal is to pass legislation in the 110th Congress that defines a practical, science-driven approval pathway for biogenerics. Collectively, members of CBI will stand together on the key principle that timely approval and timely commercialization of biogenerics will create savings to publicly-financed health care programs, and will accelerate research and development of new and improved life-saving medications.

As a pharmacologist, I have spent 27 years in drug research and development at mature pharmaceutical companies in combination with my experience at an early-stage company like Insmed. —I entered this field because I understand complex molecules, and I have dedicated my work at Insmed to helping patients with rare disorders. The scientific advancement in the biotechnology field has been tremendous, and as the CEO of a small biotechnology company whose goal is to provide therapeutic products for metabolic and endocrine disorders, it is my mission to utilize the scientific experiences and capabilities of our industry to bring medicines to patients where there is an unmet medical need. My goal is to extend our mission to include working with the backbone of the biotech industry the researchers, contract manufacturers, and like-minded small research and development companies to unleash our scientific expertise in developing biogenerics.

As I learned about Congress' interest and role in creating a biogenerics market, I felt compelled to contribute to the creation of a platform for our coalition to educate Congress about the burgeoning interest among smaller biotechnology companies to compete in a biogenerics market. I believe we all agree that when a generic version or multiple versions of a therapy are available, competition will drive down overall cost of these life saving medicines. —The development of biogenerics will create an explosion of both investment and innovation in the biologics market.

Innovation is at the core of biotechnology and solving the mysteries of disease is the goal of our industry. Unfortunately, protecting monopolies and the financial bottom line has had an impact on this mission. Our hope is Congress will allow the FDA to evaluate biogenerics on the basis of scientific facts and not the politics of the bottom line. In addition, small biotech companies often face financial hardship due to the high cost of development, but with the ability for small biotech to compete in the biogeneric market, they will have a source of revenue to invest into research and development of new and improved therapies.

In 2005 Insmed received FDA approval for the drug, IPLEX, to treat children with a rare growth disorder. IPLEX is a recombinant protein product that is similar in complexity to many of the recombinant protein products that are the topic of discussion regarding biogenerics.

We believe our experience with the development and approval of IPLEX has positioned us to successfully manufacture biogenerics. Insmed has developed the infrastructure for the manufacture, preclinical and clinical evaluation and approval of recombinant proteins that we now want to leverage for the development of generic recombinant proteins. We have the scientific and technical experience, the personnel, and the facilities to be able to produce safe and affordable generic biologics. I believe our experience with IPLEX is very illustrative of the scientific and technical issues confronting biogeneric drug developers, issues such as comparability testing and the nature of clinical data needed to support characterization of a biogeneric product. The same scientific approach we applied to the development and approval of IPLEX can be applied to the development of biogenerics.

I believe the scientific expertise and capability exist for many companies to manufacture safe and affordable biogeneric products. During the development of IPLEX, Insmed gained valuable experience in the manufacture and clinical development of recombinant protein products. We have developed expertise in all aspects of the manufacture of a protein product and in the many analytical assays that are used to structurally characterize proteins and ensure potency and purity. Insmed implemented several manufacturing changes during the development of IPLEX, including a change in the cell line used to produce IPLEX. The impact of the manufacturing changes was assessed by comparability testing in which extensive analytical tests were used to determine if any changes to the product resulted.

Insmed also developed several clinical approaches to establish safety and efficacy during the development of IPLEX. These included pharmacokinetic studies to determine the level of product in the blood and how long it lasts and pharmacodynamic studies that were short-term to determine the effect of the product on a specific relevant clinical marker. Pharmacokinetic studies, and in some cases pharmacodynamic studies can also be useful to assess comparability. These short-term clinical studies were used together with several analytical tests to determine any potential differences in the product after a manufacturing change. Our experience with IPLEX also gave us expertise in longer-term clinical outcome studies and in assessment of immunogenicity, which measures potential antibodies to the IPLEX protein.

One might ask how our expertise in the production of one recombinant protein product would allow us to develop any generic protein. Although the manufacture of each product is unique they all share the same types of manufacturing processes and the same internal quality control systems are used to monitor these processes. The manufacturing procedures for different proteins have more in common than they are dissimilar. For example, the same basic technologies and principles are applied to the fermentation, expression and purification of any recombinant protein product. We would not need information on the manufacturing methods used for the brand product but instead would use our expertise and tailor it to the specific generic protein of interest.

There is a similar ability to leverage one's knowledge regarding structural and analytical characterization of one protein to the development of a generic protein. While the types of analytical tests are tailored to each product there are well established batteries of tests that are common for proteins. One would not need the exact test methods or specifications set by the innovator company that were used to standardize the brand product. In fact, some of the tests used on the brand product may well be outdated. Since analytical technology has advanced considerably over the last 20 years, there is a real possibility that a generic protein drug will have a more robust characterization than its innovator product.

There is sometimes a misconception that the skill and expertise of generic manufacturers is less than that of brand manufacturers. I assure you that at Insmed, our personnel are highly skilled and have years of experience in manufacturing recombinant protein products. Many of our employees came from the brand industry and

were involved in the manufacture of the brand products that are now under consideration as biogenerics. We retain a highly skilled workforce.

Brand companies have been quick to point out that sometimes things can go wrong during a manufacture of a recombinant protein product. That is true and I do not know of any industry where occasional errors do not happen. However, it is critical to understand that there are safeguards that prevent any potential errors from ever affecting the safety of the product. Patient safety must be paramount. One of these safeguards is that every manufacturer must follow strict Federal laws and make their product according to Good Manufacturing Practices, which mandates multiple internal controls and the establishment of precise product specifications. Further safeguards are provided by FDA in that the FDA thoroughly reviews the manufacturing process, the test methods and the quality and integrity of multiple batches before it would approve any product, whether brand or generic. The FDA also inspects the manufacturing facility before approval and at regular intervals after approval to assure the quality and integrity of the product, the manufacturing facility and compliance with good manufacturing processes. There is no reason to believe that a generic biologic would be of a lesser quality and less safe than a brand product. The FDA has only a single standard to approve safe and effective products.

You have heard that the science exists to allow for the safe production of biogenerics. I have told you that Insmed, like many other companies, currently has the expertise and capability to produce biogenerics. What is lacking at this time is legislation that provides the regulatory pathway. We need a pathway for biogenerics that gives the FDA authority and flexibility. The FDA can determine the scientific issues and the amount of data required for the approval of biogenerics on a case-by-case basis.

We expect the FDA to issue general guidance documents at some time regarding biogenerics, but guidance documents are not absolutely necessary. Furthermore, we would not wait for the issuance of guidance before submitting applications to the FDA. Insmed believes that close interaction and dialog with the FDA on a case by case basis would allow a more robust approval process than would result from a broad guidance system. At Insmed, we have shown that we can successfully work with the FDA and plan to continue to work closely with the FDA during the development of future biogeneric products.

In summary, we have seen that the science is there for biogenerics. The expertise and capability also exists for the manufacture of biogenerics. However, the regulatory pathway is not available and we are asking you to support legislation that would create such a regulatory pathway. This would allow not only Insmed to make safe and affordable biogenerics available to the American public but would open the floodgates for all the small biotech firms with the drive, technology, and know how necessary to create a new and competitive biogenerics industry that will generate savings and new innovation for all.

Mr. PALLONE. Thank you. Mr. Kingham.

STATEMENT OF RICHARD F. KINGHAM, PARTNER, COVINGTON & BURLING

Mr. KINGHAM. Thank you very much, Mr. Chairman. I am a partner in Covington & Burling. I am assigned to both the Washington and London offices, and my practices involves regulation of biologics and biotechnology products under both U.S. and European community law.

I submitted a prepared statement that discusses in detail the criteria that ought to be applied in establishing a legislative pathway for follow-on biologics and also summarizes the European community experience with establishing a system for so-called similar biological medicinal products.

In my time now, I would like to focus on a single criteria that I believe any such system should satisfy and that is the need for a substantial period of non-patent data exclusivity. Now, this is a period of time during which follow-on applicants may not rely on the safety and effectiveness data submitted by an innovative manu-

facturer in support of a reference product. Every developed nation in the world has such a period of time that it allows for medicinal products. Data exclusivity serves a different purpose from patents. Patents protect inventions, any sort of invention, and they are available for any type of product and indeed for things that are not even products. Innovative medicines present a special societal issue, and that is the need to do lengthy, expensive and commercially risky studies to demonstrate their safety and effectiveness to meet FDA approval requirements. Today it takes about 15 years from the time of the original invention to bring a new biotechnology product to market, and the fully allocated costs of research and development are estimated to be about $1.2 billion per product. Even with all this, there is no guarantee that a particular product will get to market or that it will recover R&D costs if it does. Investments and risks of this magnitude are I think unique to the pharmaceutical industry. Whether or not patents are available to protect products of this kind, society has a profound interest in assuring that there are adequate incentives to do the studies necessary to bring these products to market.

Now everything I have said up to now is applicable really to all pharmaceutical products, though some of the figures for timing and cost may be greater for biotechnology drugs. But there are special issues posed by biotech products which I believe more clearly justify a substantial data exclusivity period.

Under the Hatch-Waxman Act as applied to small-molecule drugs, a generic product for which an abbreviated new drug application, or ANDA, is filed must contain an active ingredient which has demonstrated to be the same as or identical to that of the referenced drug upon which it relies. This means that if there is a patent for that active ingredient and that patent is valid, it is likely that that applicant will run head on into the patent which protects the referenced product and therefore the referenced product will enjoy a period of effective market exclusivity equal to the life of that patent.

But under any legislative pathway, and I refer not simply to the one that Representative Waxman has proposed, but any scientifically reasonable approach to the issues presented by follow-on biologics, it will in fact be necessary to allow FDA the discretion to consider applications for products which are similar to but not identical to the referenced products. Dr. Woodcock explained the scientific reasons why that is true, and that means that the possibility exists for different processes and different structures to be used in producing the active ingredients of follow-on products so that they will avoid the protection of both product and process patents that protect the innovator. This creates the real potential for patents not to serve the same protective market purpose that is served by patents for small-molecule drugs under Hatch-Waxman.

Now that is the biggest point, but there are subsidiary points. Increasingly, for example, the Patent and Trademark Office and the courts have required that the patent applications, the claims for biotechnology products be even more narrowly drawn than in the past, thereby increasing the plausibility that people can make small changes in the structure of follow-on products and avoid the patents for the innovative product. And even if a patent contains

claims which cover a wide variety or an extensive variety of molecular structures, if patent term restoration is granted, it will apply only to the specific molecule that was approved by FDA, not to the other structures that may be covered by broader patent claims. And of course, we saw only last Monday in KSR against Teleflex that the Supreme Court is increasingly scrutinizing that patents should be granted at all and applying a tougher standard with respect to what constitutes a significant innovation that warrants protection under the patent laws.

Now, these are all very legitimate issues for patent lawyers to be concerned with and for policy discussions to be held about. But whatever we decide with respect to the scope of patents, there remains an overwhelming need of society to provide the incentive for the studies necessary to develop these products. What is the period of time that should be provided? Well, the Congress said in 1984 that an effective patent life of 14 years a period of market exclusivity guaranteed by the patent life of a drug was the appropriate time. If patent protection is not fully adequate, and I think it may not be, then I think the period of 14 years is still the right number.

Thank you very much.

[The prepared statement of Mr. Kingham follows:]

Statement of Richard Kingham
Partner, Covington & Burling
Subcommittee on Health
House Committee on Energy and Commerce
May 2, 2007

Mr. Chairman and members of the Committee, thank you for inviting me today. My name is Richard Kingham, and I am a partner assigned to the Washington and London offices of the law firm of Covington & Burling. I regularly represent manufacturers of innovative pharmaceuticals and biotechnology-derived medicines.

Since entering law practice in 1973, I have participated in numerous legislative and regulatory proceedings relating to biological products, including the Swine Flu legislation in 1976, the National Childhood Vaccine Injury Compensation Act in 1986, and recent legislation relating to countermeasures against bioterrorism and pandemic influenza. I took part in the regulatory process relating to several of the first biotechnology-derived medicines in the 1980s and participated in proceedings relating to orphan drug exclusivity for biotechnology products in the late 1980s and early 1990s. I assisted pharmaceutical manufacturers during legislative proceedings leading to enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (the

Hatch-Waxman Act). For the past 17 years, I have acted for pharmaceutical companies and associations in connection with regulatory matters in the European Union, including recent legislative and administrative proceedings relating to similar biological medicinal products, or biosimilars. I have taught pharmaceutical law at the University of Virginia and Georgetown University law schools and at Cardiff University and the University of Wales in the UK, and have served as a member of committees of the Institute of Medicine of the National Academy of Sciences and the National Institutes of Health.

1. Basic Principles for a Regulatory Framework for Biosimilars

As the title for this hearing implicitly recognizes, any legislation creating a pathway for follow-on biological products must be designed to protect patient safety and to preserve incentives for development of new medicines. More specifically, the statutory framework should:

- Ensure that follow-on products are reviewed under the same criteria that apply to innovative products -- based on proof of safety, purity, and potency, as well as adequate manufacturing facilities and controls.
- Recognize that follow-on biologics are not generic drugs. Biologics contain complex active substances manufactured in living systems, so that there will inevitably be differences between follow-ons and reference products that can affect their safety or effectiveness.

- Accept that biological products -- unlike generic drugs -- cannot be approved on the basis of physical and chemical tests of the active substance and bioequivalence studies of the finished product in a small number of healthy subjects. Instead, substantial preclinical testing and clinical studies will be required, including comparative clinical trials to determine whether there are significant differences between follow-ons and reference products in terms of safety and effectiveness. Special attention must be paid to the potential for immunogenicity.
- Provide open, public procedures for all stakeholders to participate in the development of criteria for the approval of follow-on products. Manufacturers of reference products have unique knowledge and experience that should be available to the Food and Drug Administration as it develops requirements for testing follow-on products.
- Acknowledge that, because follow-on biologics will inevitably differ from reference products, it is not possible, in the present state of science and technology, to treat them as interchangeable. This has been clearly recognized by FDA, which stated in a recent submission to the World Health Organization that it "has not determined how interchangeability can be established for complex proteins." If products are deemed interchangeable, patients may be switched from one product to another without the knowledge of the prescribing physician, a situation that would be unacceptable for biosimilars in the current state of science and technology, because they will likely differ from reference products (and from each other) in safety and effectiveness.

- Give FDA clear authority to require measures after approval, including enhanced pharmacovigilance systems, antibody testing, and other studies, to detect rare but serious side effects, such as immunogenicity, that cannot be detected in reasonable programs of pre-market testing.
- Assure that follow-on biologics will be given distinct names, to enable regulators to distinguish them from reference products (and other follow-ons) when evaluating large quantities of data from adverse event reports, which will serve as one of the main mechanisms for detecting differences in the occurrence of rare but serious side effects.
- Include a substantial period of non-patent data exclusivity, during which follow-on applicants may not rely on safety and effectiveness data submitted by the innovator, in order to provide incentives required to bring new biotechnology products to market. The necessary incentives cannot be supplied by patents alone. Data exclusivity and patents serve different purposes. Patents reward inventions, but provide no guarantee that those inventions will be commercialized. For biotechnology products, the initial invention that yields a patent application occurs very early in the research and discovery stage. There follows a lengthy, expensive, and commercially risky period of pre-clinical tests and clinical trials required to determine whether a product derived from that invention will be safe and effective. The whole process typically takes 15 years and entails an investment of $1.2 billion or more, with no guarantee that the end-product will reach the market, or recoup research and development costs if it does. Whatever the strengths or weaknesses of patent protection, society has a

profound interest in creating the incentives necessary for companies to make the investments in research and development required to bring new biotechnology products to patients. A substantial period of data exclusivity is especially important for biotechnology products, because patent protection is often less robust than for small-molecule drugs. Many biotechnology products are protected primarily by process patents or relatively narrowly drawn product patents that may be susceptible to work-arounds, especially under a regulatory regime for biosimilars that permits follow-on products to differ in their structural features from reference products. Ideally, the period of data exclusivity should equal the period of market exclusivity that was contemplated by Congress under the patent term restoration provisions of the Hatch-Waxman Act (14 years), to avoid skewing investment away from biotechnology innovation. I have attached to my testimony a more detailed paper prepared by the Biotechnology Industry Organization, which explains why such a period of data exclusivity is both necessary and justifiable.

- Respect intellectual property and other legal rights. Follow-on biologics legislation should not undermine the patent rights of innovators or diminish protection of trade secrets.

2. *The European Experience*

The European Union system for approval of similar biological medicinal products, or biosimilars, is broadly consistent with these criteria. It comprises a series of

legislative enactments, guidelines, and policy decisions which, taken together, clearly recognize that the requirements for approval of ordinary generic drugs are not appropriate for biosimilars.

Public proceedings to develop data requirements -- Detailed requirements for data submitted in support of applications for biosimilar products have been developed in public proceedings, leading to general guidance for all biosimilars, more detailed guidance on biotechnology-derived proteins, and guidance for specific product types, such as human insulin, human growth hormone, and erythropoietin. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has established a special working party, composed of experts from the various EU member state governments, to develop these guidance documents. The CHMP typically begins the process by issuing a "concept paper" that identifies the topics it believes should be addressed in a guidance document, and providing interested persons several months to submit detailed comments. Taking account of these comments, the working party then prepares draft guidance documents, which are issued for public comment and circulated to the medicines agencies in all EU member states. This process has ensured that all stakeholders have an opportunity to participate in the development of detailed requirements for follow-ons, and that the EMEA has the benefit of experience that is uniquely available to innovative manufacturers and others outside the Agency. In several cases, draft guidelines have been substantially modified following the public comment period. Public proceedings have, moreover, not significantly delayed the

approval process in Europe. Most guidance proceedings have been completed in approximately a year.

Requirement for clinical testing -- Detailed requirements have been tailored to each product class, but all guidelines issued to date have required comparative clinical trials in addition to physical and chemical assays and pre-clinical tests. Two products have been approved to date, and in both cases substantial comparative clinical trials were required. One application was disapproved, in large measure because data from clinical trials showed that there were significant differences in safety and effectiveness in comparison to the innovative product. It is important to note that these differences would not have been detected prior to marketing but for the requirement to conduct comparative clinical trials.

Special requirements for immunogenicity testing -- The EU has placed special emphasis on measures to detect immunogenicity. This is understandable, because a significant number of patients in the EU suffered from pure red cell aplasia, a rare but very serious side effect caused by a seemingly minor formulation change in one dosage form of an erythropoietin product. In addition to requirements for antibody tests and other measures prior to approval, the EU has required post-marketing tests or enhanced pharmacovigilance activities.

Biosimilars not regarded as generics -- Although the European Medicines Agency does not make therapeutic equivalence determinations (this is instead done

country-by-country, according to varying rules), its guidance on biosimilars states that they should not be regarded as "generics." EU member states that have considered the issue to date have determined that biosimilars should not be substituted for reference products.

Incentives for research and development -- Finally, the EU has ensured that there are substantial incentives for innovative companies to invest in research and development of new biotechnology products. Biosimilar products cannot enter the market until 10-11 years after reference products are approved, and innovators retain all their rights under EU patent laws, including remedies for infringement.

In summary, the European Union has struck a reasonable balance that provides incentives for innovative research and development, provides a clearly delineated pathway for approval of follow-ons after exclusivity periods expire, and ensures that follow-on products will be safe and effective.

3. Applying Lessons from the EU Experience in the United States

Although the European experience is instructive, the EU regulatory system cannot be transferred verbatim to the U.S. legal and political environment. For example, the primary legislation on which the EU system depends is, by U.S. standards, very short and succinct. This is in part because the European Commission, which drafts the legislation, is also ultimately responsible for the approval of biotechnology

products. The guidance documents that are key to the European approval system were already under development before the legislation was adopted, and all parties knew how the process would work. Under the U.S. system of separation of powers, Congress must provide more specific instructions to FDA if it wishes to achieve a result similar to that in the EU. It is for this reason that most provisions of U.S. drug law enacted in recent years are far more prescriptive than their counterparts in Europe. The provisions of the Hatch-Waxman Act governing abbreviated new drug applications are, for example, much more detailed than counterpart provisions in EU law governing generic marketing authorization applications. Similarly, for innovative products, Congress has mandated a specific type of evidence of effectiveness ("adequate and well-controlled clinical investigations"), while EU law contains only a general requirement for proof of efficacy. (This standard for proof of effectiveness, established in U.S. law under section 505 of the Federal Food, Drug, and Cosmetic Act, is equally applicable to biologics, because of provisions in relevant legislation providing for harmonization of approval requirements for drugs and biologics.)

Action-forcing mechanisms and dedicated funding may also be appropriate to ensure that FDA has the incentive and resources to develop guidance documents in consultation with relevant stakeholders. A new advisory committee may be appropriate to provide the kind of independent expert advice that the EMEA receives from the expert working party within the CHMP and from national authorities around the EU.

Nor should the United States assume that the data exclusivity period recognized in EU law provides the incentives required in the U.S. marketplace. Congress determined in 1984 that, in order to provide adequate incentives for research and development of important new medicines, the appropriate period of market exclusivity for pharmaceutical products should be approximately 14 years (the maximum effective life for a patent extended under the Hatch-Waxman Act). A strong case can be made for a similar period of data exclusivity in any approval system for biosimilars, because, as noted above, patents alone are unlikely to provide the certainty and predictability required for investments needed to bring new biotechnology products to market.

4. H.R. 1038 -- "The Access to Life-Saving Medicine Act"

Advocates of H.R. 1038 -- the "Access to Life-Saving Medicine Act" -- have suggested that the bill takes account of the EU experience. Unfortunately, in almost every important respect, the bill takes an approach that departs significantly from that taken in Europe, and from the basic principles that should govern any legislative framework for biosimilars. For example, H.R. 1038:

- Provides no mechanism for public comment or participation in the development of requirements for approval of biosimilars. Instead, requirements would be determined in private license application proceedings between individual applicants and FDA, and the bill actually includes provisions to discourage efforts

by innovative companies and other interested persons to bring scientific data and information to the Agency's attention.

- Does not require clinical testing of biosimilar products. In fact, the bill contains provisions that are intended to discourage FDA from requiring such tests.
- Requires FDA to treat the active substances of biosimilars as "highly similar" to reference products when their structural features are actually significantly different, and even permits FDA to approve follow-on products that are not deemed "comparable" to reference products on which they rely.
- Limits FDA's power to require post-market testing of biosimilars to detect rare but serious adverse events, including immunogenicity, that cannot be detected in pre-market testing.
- Requires FDA to make interchangeability determinations without first conducting public proceedings to determine what the requirements should be, and even if the Agency has not yet decided that such determinations are scientifically possible.
- Provides no period of protection for valuable safety and effectiveness data submitted by innovators. Follow-on applications, relying on innovators' data, could be filed immediately after innovative products are approved.
- Makes one-sided changes in the patent laws that favor follow-on applicants at the expense of innovators, including provisions for compulsory licensing under innovator patents.

Conclusion

In conclusion, I would urge the Committee to give careful consideration to the European experience in developing any pathway for follow-on biological products in the United States. Whatever model is chosen, however, it must protect patient safety and preserve incentives for research and development of new therapies. The United States today is the undisputed world leader in biotechnology-derived medicines. Congress should aim to ensure that any legislation creating a pathway for follow-on biologics does not undermine our leadership position.

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A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY[1] WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES

BIO recognizes the importance of providing the fruits of science and innovation in healthcare for the benefit of all American citizens. BIO represents both small and large biotechnology companies: some with products already on the market and most with their lead products still at the development stage with many years ahead of them before they can expect marketing approval. BIO's goals are to ensure that those companies with approved products are able to receive an appropriate return on their investment, and that the development stage companies can continue to finance their operations through accessing the venture and equity markets with the opportunity for an appropriate return in the future. This enormous reservoir of innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients.

Central to achieving these goals, any statutory pathway for follow-on biologic products ("FOBs") must establish a substantial period of data exclusivity to preserve incentives for research, development, manufacture, and approval of new biologic therapies. This is necessary because, under a statutory framework allowing for FOBs, there is a very real potential that the manufacturer of a FOB may be able to secure abbreviated regulatory approval based at least in part on the innovator's prior approval, and, at the same time, avoid infringing patents that protect the innovator's biotech product. That likelihood exists because of the confluence of two critical factors not present in the Hatch-Waxman construct for generic small molecule drugs. First, unlike a generic drug which must be the same as an innovator product, a FOB will only be required to be "similar' or "highly similar" to the corresponding innovator product. Second, because of the nature of biologic products – large molecules produced by living cells and organisms – patent protection is often narrower and easier to "design around" than that afforded to small molecule drugs.

In light of this gap in patent protection for biologics, data exclusivity in a FOB regime must be substantially longer than the five years currently afforded to drugs under the Hatch-Waxman Act. Biotechnology companies must have some certainty that they can protect their investment in the development of new breakthrough therapies for a substantial period of time in order to secure the necessary resources from venture capital firms and other funding sources. As described below, that period should be no less than 14 years if biologics are to receive the same length of effective

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[1] Definition of data exclusivity: the time period after approval of the innovator's product during which the FDA may not approve a follow-on biologic product relying to any degree on the safety and effectiveness of the innovator product.

market protection as drugs, and thus avoid skewing investment away from higher risk biologics research and development. Indeed, in striking the appropriate balance, Congress should err on the side of protecting incentives for biomedical innovation because, as compared to the broader pharmaceutical industry, the biotechnology industry is largely comprised of small companies that are, for many reasons discussed herein, more vulnerable to changes in investment incentives.

The Need for Substantial Data Exclusivity for Innovator Biologics in any FOB Statutory Scheme

The Problem: The Similarity Standard for FOBs Creates a Gap that May Allow for Regulatory Approval without Adequate Patent Protection

Under the 1984 Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, a generic version of a small molecule drug may be approved for marketing only if its active ingredient is the "same" as in the innovator product. Thus, the patents that cover the innovator's drug molecule necessarily apply to the duplicate, generic version, and a generic may not enter the market until the innovator's patent expires. Indeed, the manufacturer of a generic drug may not have it both ways – it cannot gain FDA approval of its product by demonstrating that the active ingredient is the same as the innovator product and then turn around and claim in the patent context that its product is different from the innovator's drug. In this respect, the Hatch-Waxman exclusivity provisions work in concert with the patent system to provide market protection to innovator drugs.

In contrast, under the statutory framework being considered for FOBs, the same level of protection will not be available to innovator biological products. Unlike a small molecule generic drug, a FOB will not be required to be the "same" as the innovator product. Instead, it will only have to be "highly similar" to the innovator product. While the meaning of "highly similar" may vary between legislative proposals, there is no question that it falls short of the degree of sameness required of generic drugs. In fact, under one current legislative proposal, "highly similar" is defined in a manner that would allow for approval of FOBs with potentially significant differences from the innovator product. As a result, a FOB may be sufficiently similar to the innovator biologic to rely to some degree on the safety and effectiveness of the innovator product and thus receive abbreviated regulatory approval. Yet, it may still be different enough from the innovator product to avoid a patent infringement claim and, thus, get on the market well in advance of innovator patent expiration – undermining incentives to invest in innovation. The pace of medical advancement and the patients who stand to benefit from it would likewise suffer.

The Gap in Protection for Innovator Biologics Will Widen as Patent Law Yields Increasingly Narrow Patent Claims

Because of the nature of biologic products – produced by living cells and organisms – patent protection is different from and may be weaker than that afforded to small medicinal molecules.[2]

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[2] This is so because the so-called "utility," "written description," and "enablement" requirements of the Patent Act are interpreted more stringently for biotechnology inventions than for most (continued...)

First, because of current limitations of patentability of naturally occurring substances, many biologics are protected only by process patents that may be easier to "design around." Moreover, under rules of patentability specific to biotechnology inventions, patent claims on biologics must often be narrowly drawn to the specific innovative aspect (e.g., a specific protein or nucleotide sequence) to be allowable. By contrast, patents on small medicinal molecules can often claim a whole class (a so-called genus) of related molecular structures and thereby provide a "penumbra" of patent protection covering the innovator small molecule.

These distinctions in patent protection for biologics are especially significant because, through a series of court decisions, the patent law is leading inexorably to narrower allowable claims. While this trend impacts all products, it is especially relevant to questions surrounding protection of innovator biologics in a FOB regime. That is because narrower patent claims for such products will result in a wider gap through which a FOB may be able to receive regulatory approval while still eluding an innovator's patents.[3] Furthermore, the sheer size of biologic products – often several hundred- or thousand-fold larger than small molecule drugs – increases the number of possible ways of altering the product such that it would be similar enough to the original product to qualify as a FOB but different enough to be outside the scope of the patents on the original product. Disputes over patent claim coverage that are likely to arise from this situation would lead to an increase in litigation expenses and add to the uncertainty that biotechnology companies could protect their investment.

Strong Data Exclusivity Will Preserve the Balance that Congress Found Necessary to Stimulate Innovation in the Pharmaceutical Industry

With passage of the Hatch-Waxman Amendments in 1984, Congress recognized that normal patent protection alone is insufficient to provide small molecule pharmaceutical innovators with sufficient market exclusivity to allow them to recoup clinical research and development costs. To address this problem, Congress established a period of data exclusivity for drugs, and it created a mechanism allowing for the extension of patents on innovator drugs and biologics for up to 14 years following approval of the product.[4] In providing for patent extensions of up to 14

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other technologies. Moreover, patents cannot claim something that occurs naturally. Therefore, because many biotech products are "artificial" (recombinant) versions of naturally occurring proteins, the patent claims must be narrowly crafted (i.e., limited to specific isolated and purified DNA sequences, proteins, or clonal cell lines) in order to avoid encompassing naturally produced molecules. In contrast, most of the small medicinal molecules are synthetic. It is in part because they never existed before in nature that the claims to such synthetic small molecules may be drafted more broadly than claims to biotechnology products.

[3] Manheim, Granahan, and Dow. "'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry," Health Affairs, March/April 2006.

[4] Extension is calculated by taking: ½ of the time spent diligently from IND effective date to NDA submission; and the full NDA review period; patents cannot be extended by more than 5 years. The patent extension also cannot result in a patent that has a term of more than 14 years post-NDA approval.

years, Congress acknowledged that – unlike most other industries – the pharmaceutical industry rarely benefited from the full length of normal patent protection (then 17 years) due to the long development and regulatory approval process for drugs. Given that Congress has previously concluded that 14 years of patent protection is appropriate for drugs and biological products, any statutory formula that allows for FOBs should at least guarantee that same degree of effective market protection – and, for the reasons discussed above, that protection can be accomplished most predictably through data exclusivity.

The presence of substantial data exclusivity also would serve as an additional incentive to research and prove the safety and effectiveness of new indications for existing biologics. Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time. It is important to provide substantial exclusivity for the original treatment in order to support the expensive further development for these later indications, as well as an additional period of exclusivity – no less than two years beyond the standard 14 year period – to provide the proper incentives to research and bring to market the vibrant pipeline of treatments that can allow cancer patients to live longer and healthier lives.

It also is important to note that this length of data exclusivity for innovators in any FOBs regime would not operate as an extension of exclusivity. Rather, the period of data exclusivity would run concurrently with the patent term for the product, which itself may run at least 14 years. Data exclusivity would create actual market protection for the innovator product only in those instances where the follow-on manufacturer is able to work around the patents held by the innovator but still gain approval of its product as a follow-on. In this respect, a 14-year period of data exclusivity serves essentially as an insurance policy that provides the innovator with some certainty of protection, given that a FOB can be approved on the basis of a less stringent standard of similarity. Thus, 14 years of data exclusivity is an essential component of a balanced statutory pathway for FOBs, making possible their introduction and use in the market while appropriately safeguarding incentives for biotechnology innovation.

Empirical Data Support a 14-Year Period of Data Exclusivity for Biologics

In 1998, the Congressional Budget Office found that the average period of time for marketing of a drug product with patent protection is 11½ years.[5] Further, new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.[6] Yet, as described below in more detail, it is well established that the costs and risks of developing biotech products are generally higher than for drugs. For example, average clinical development

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[5] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

[6] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics (*forthcoming*).

times for biologics have been found to exceed development times for small molecule drugs.[7] As a result, it is essential that the period of effective market protection for drugs – 14 years – be extended to biologics. Indeed, if the data exclusivity period for biologics is less than that, then, because of the higher risks of biologics development, it will skew investment options away from biotechnology.

Strong Protection for Innovative Biologic Products Is an Essential Incentive for Investment in Biomedical Innovation

In crafting a FOBs regime, it is important to err on the side of incentivizing innovation due to the unique elements of the biotechnology industry, which is largely comprised of small, privately-funded start-up companies without reliable revenue streams. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted FOBs regime.

Biotechnology Companies Bear Enormous Costs and High Uncertainty

- Cost of Capital: The cost of capital for small biotechnology companies is much higher than the cost of capital for large pharmaceutical firms. While large pharmaceutical companies have product revenue streams that they reinvest in the research and development of new pharmaceuticals, the vast majority of biotechnology companies, as shown below, do not have any marketed products and have very limited revenues.

  The lack of a product revenue stream coupled with risk of early product development drives up biotechnology companies' cost of capital:

  - Whereas the cost of capital for a large pharmaceutical company averages 15.7%, biotechnology companies with at least one drug approved have an average cost of capital of 18.7%
  - Biotechnology companies with only a drug candidate in clinical phase II or III trials have a cost of capital averaging 27.4%.[8]

  The higher cost of capital coupled with failure to give an adequate data exclusivity period to biotech products could result in shifting investment away from small, innovative biotechnology companies.

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[7] Tufts Center for the Study of Drug Development. http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69
[8] Grossmann, Martin. Entrepreneurship in Biotechnology, Physica-Verlag NewYork, 2003.

- Production Costs: Biologics, as opposed to pharmaceuticals, are produced using biologic processes such as cell cultures or fermentation and are then purified. Indeed, cell culture facilities:

    - Take on average three to five years to construct
    - Cost between $250 million and $450 million
    - Must often be constructed before drugs enter clinical testing[9]

    Further, the cost of materials to produce a biologic is 20 to 100 times more than the materials used to produce a small molecule pharmaceutical.[10]

- Manufacturing Uncertainties: Biologics manufacturing necessitates far more planning, investment and skilled personnel and, thus, can be much riskier than small-molecule manufacturing.[11] "A typical manufacturing process for a chemical drug might contain 40-50 critical tests. The typical process for a biologic, however, might contain 250 or more critical tests...Consequently, construction and validation of new facilities is disproportionately expensive and time-consuming."[12]

- Late-Stage Failures: The success rate for late-stage biotechnology products is lower than for pharmaceuticals. From 2001 – 2005, the success rate of a Phase III trial for the average pharmaceutical was 65% to 75%; whereas, the success rate of a Phase III trial for biotechnology produces was 54% to 58%.[13] These failures occur at the last stage of product development – after years of research and hundreds of millions of dollars have been spent.

The Biotechnology Industry is Comprised Mostly of Small, Start-ups

The biotechnology industry in the U.S. is still relatively nascent: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies—many of which will never see a product come to market or turn a profit—that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology*

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[9] Grabowski, Henry, Iain Cockburn and Genia Long. "The Market for Follow-On Biologics: How Will It Evolve?" Health Affairs, 25(5).

[10] U.S. Bancorp Piper Jaffrey. "The Road Ahead for Biologics Manufacturing," January 1, 2002.

[11] Lakshmikanthan, Jayant. "Outsourcing: Biologics Manufacturing: The CMO Advantage," International BioPharm, Feb. 1, 2007.

[12] Webster, Christopher, et al. "Can There Be an Abbreviated Applications, Generics or Follow-On Products?" BioPharm International, July 2003.

[13] Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.

companies (all biotechnology companies but the top ten) account for two-thirds of the industry's clinical pipeline.[14]

The statistics speak to the challenges this emerging industry faces: in 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:[15,16]

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Net Loss ($B)	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	4.1

A 2006 Biotechnology Industry Organization (BIO) representative survey of 300 small biotech companies showed:

- **Company Size:** 65% of the companies surveyed have fewer than 50 employees. 40% of the respondents reported that their company's revenue from all sources was less than $150,000 in the previous year, and 66% had revenues under $1 million annually. Additionally, of those companies that do have revenue, the only revenue streams for the vast majority of the companies were milestone and royalty payments.

- **Product Development:** Of the companies surveyed, less than 10% have a product on the market. The chart below shows the distribution of latest phase of lead product development, which represents each individual company's most fully developed product:

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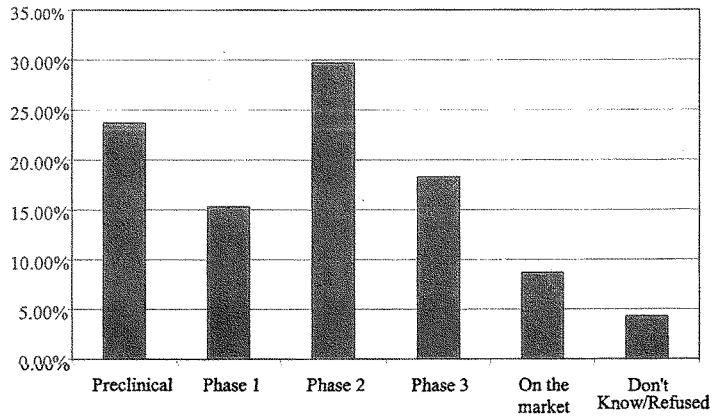
[14] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

[15] Ernst and Young LLP, Annual biotechnology industry reports, 1995 – 2006. Financial data based primarily on fiscal-year financial statements of publicly traded companies.

[16] Only about 20 biotech companies are currently profitable: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

Latest Phase of Lead Product Development



Thus, while the biotechnology industry continues to grow and expand, the vast majority are emerging enterprises, relying on the investment community and the talents of their dedicated employees to bring much-needed treatments to fruition. Failure to provide substantial data exclusivity could fundamentally alter the ability of these small companies to continue to innovate.

U.S. Public Policy Should Encourage a Growing Biotechnology Industry

The U.S. leads the world in biotechnology innovation:

	U.S.	Europe	Canada	Australia
Annual R&D	$18.5 B	$4.2B	$1.7 B	$1.0 B
No. of Companies	1,473	1,878	470	226
No. of Public Companies	363	96	81	58
No. of Employees	146,100	32,470	7,440	6,393

Source: Burrill & Company, Ernst & Young

Indeed, the per capita biotechnology R&D is 574% higher in the U.S. than in the European Union.[17] U.S. public policy thus should support this important U.S. industry and employer and encourage its growth through effective market protection from unfair and premature competition by generic companies. Only in this way will the U.S. continue to lead the world in biotechnology innovation.

A. Conclusion

Continued U.S. leadership in biotechnology innovation, made possible through sound public policy as outlined here, will enable further progress in the research and discovery of breakthrough therapies to improve the health and lives of patients across the globe. Today, as the legislative framework for follow-on biologics comes into view, it is critical that data exclusivity of no less than 14-years be included as a central component of that framework, given the uncertainties of effective patent-based protection and the higher risks associated with investment in biotechnology.

[17] Based on EU's population of approximately 457 million people and the U.S. population of 298 million people – both figures estimated in July 2006.

Mr. PALLONE. Thank you, Mr. Kingham. Mr. Downey.

STATEMENT OF BRUCE DOWNEY, CHAIRMAN OF THE BOARD, GENERIC PHARMACEUTICAL ASSOCIATION, CHAIRMAN AND CEO, BARR PHARMACEUTICALS, INCORPORATED

Mr. DOWNEY. Thank you, Mr. Chairman. Thank you, Ranking Member Deal for inviting me to testify today. I have prepared a written statement and I ask that it be accepted into the record, and I would like to expand on that in just a few points.

First I would like to say that while I am chairman of the GPHA, the Generic Trade Association, I am actually appearing today in my capacity as CEO and chairman of Barr Pharmaceuticals, a company that is a member of the Generic Association and one that aspires to make generic biologics which are the subject of this hearing.

I note at the outset that we are at a historic time, and I was thinking as I came over this morning it is a 23-year cycle. In 1938, the Food, Drug, and Cosmetic Act was amended to require drugs be proven to be safe. Actually 22 years later, the Kefauver amendment required they be proven to be effective. Twenty-two years after that the Hatch-Waxman bill adds a pathway for generic pharmaceutical products, and we are here in 2007, 23 years later we hope to add a pathway for generic biologics.

And I think we have reached an amazing consensus over the last 2 or 3 years hearing members of the committee on both sides of the aisle, the number of organizations listed by Congressman Waxman in his statement, there really is an emerging consensus that it is not whether there should be a pathway but what that pathway should look like and what other provisions it should contain. I think we all agree or could agree that safety is the number one issue, and we as a potential manufacturer of generic biologic product certainly want to manufacture safe and effective products. So we don't disagree with that at all. And we think FDA is the proper arbiter of what safety standards should be applied.

We also think there should be a balance between those in the innovator industry and those in the generic industry, a balance similar to the one struck in the Waxman-Hatch Act. And there were two provisions in that Act that dealt with exclusivities and rights of innovators. One was the patent term restoration component which as a formula to add patent life to products were lost in regulatory review, and I point out that that patent term restoration provision not only applies to pharmaceutical products but applies to the biologic products developed by innovators. So they have already got the prepayment on the biologic side of the patent term restoration features of Hatch-Waxman.

Now, Hatch-Waxman also included a 5-year exclusivity—and I personally don't object to that period. I certainly will disagree with the 14-year period but 5 years I think is an appropriate number and one that I could certainly support. I can't again speak for my trade association on that point. And the third is we all want to ensure that innovation is protected, and I would argue and I think correctly argue that the pathway for generic pharmaceuticals was the greatest boon to pharmaceutical innovation in history because

it forced brand manufacturers to replenish their products in the face of generic competition.

And so you look at the statistics, and I didn't prepare it for today but I certainly could and submit it if the committee wants, the rate of investment in R&D in the brand industry skyrocketed post Hatch-Waxman because of the threat of generic competition. And I think the same will happen here in the biologics business. If there is a generic pathway, you will see increased innovation and increased spending on R&D.

I would like to quickly, in my last 90 seconds, cover three points. One is that in the pathway that I think we should follow, the same standard for BLA, that is innovator biologic products, NDA's, ANDA's, and that is a pathway that is sponsor-initiated, we propose the product, we propose the clinical trial, and the FDA responds and it adds requirements or agrees as they see proper. I think that provides the great level of safety that we all seek. It also provides an efficient and flexible system that can deal with different products in different ways.

Second, I think we need to have a provision that would permit resolution of intellectual property disputes in advance of launching the product. These are very contentious issues. Many of these products do not have one or two patents, but 30, 40 patents and there are disagreements about whether we infringe or if they are valid, and there needs to be a mechanism that allows those issues to be decided before there is a launch of the product that allows both innovator and generic companies to manage the risks that they confront and it also allows for the earliest lawful entry of the product and doesn't allow the litigation post-exclusivity period, post-patent to delay the launch of a product.

And then finally I think we need to have the flexibility for the FDA to establish the requirements on an individual product basis, and I urge we reject the idea of this public hearing with all the comments and first to get a draft guidance and refine it once it is out. I think that simply delays the process, and the process currently followed where your sponsor initiated products are presented it to the FDA, the FDA comments, we carry it out, has provided safety and efficacy over all sorts of pharmaceutical and device products and would work very well here. It works for the innovators in the biologic area, and I would point out that H.R. 1038 has all three of these features and I would urge that whatever legislation comes out has them also. Thank you very much.

[The prepared statement of Mr. Downey follows:]

TESTIMONY OF BRUCE L. DOWNEY

Chairman Pallone, Ranking Member Deal and members of the House Energy and Commerce Committee Subcommittee on Health. I am Bruce Downey, the chairman and chief executive officer of Barr Pharmaceuticals, a leading global generic pharmaceutical company.

I want to thank you for convening this hearing and for allowing me to express my company's views on issues so vital to the continued success of the generic pharmaceutical industry—an industry that saves consumers and taxpayers literally billions of dollars each year in prescription drugs costs. Indeed, no other industry has made, or continues to make, a greater contribution to affordable health care than the generic pharmaceutical industry.

While my testimony today is on behalf of Barr Pharmaceuticals, I also serve as chairman of the Generic Pharmaceutical Association, which represents more than

100 generic manufacturers, distributors and suppliers of bulk active pharmaceutical chemicals worldwide. I mention my role in GPhA because it is important to note that the issue we address today—that of generic biological medicines—is at the top of the association's priority list of legislative and policy initiatives.

Mr. Chairman, this Congress holds the key that will open the door for generic and other manufacturers to provide affordable access to many of the life-saving biological medicines used in the treatment of diabetes, cancer, rheumatoid arthritis, HIV/AIDS and other diseases. Today, the cost of these treatments can put them out of reach of many consumers. The rheumatoid arthritis and psoriasis treatment Enbrel, for instance, costs an average of $16,000 a year per patient. Biological drugs for multiple sclerosis range in price from $16,000 to $25,000 a year. Neulasta, used to correct chemotherapy-induced white blood cell deficiency, costs an average $3,500 per chemotherapy cycle.

What becomes frightening from the cost perspective is that not only are the costs of biological treatments getting more expensive each year, but the utilization of these medicines is growing, as well. These two factors coupled together yields exponential growth in the amount we are spending on biologics every year.

According to the 2006 Drug Trend Report released in April by Express Scripts, biotech drug spending increased 21 percent last year, even as growth in traditional prescription drug expenditures slowed. The report showed that growth hormone deficiency spending rose nearly 23 percent in 2006 due to a 10.7 percent increase in utilization, coupled with the increase in product cost.

This dual impact of higher prices and greater utilization presents a recipe for disaster which will end in price controls. The alternative, as we are seeing in the chemical drug sector, is competition.

Thus, creating a pathway that allows for the introduction of safe and affordable generic alternatives to these medicines is vital. It not only will save consumers and taxpayers billions of dollars a year, but, again, will allow more patients access to these important medicines.

This committee is well aware of the role traditional chemical generic drugs play in helping consumers, insurers, and the government in achieving billions of dollars in savings each year. Generic drugs filled more than one-and-a-half billion prescriptions in the U.S. last year. That is nearly 55 percent of all prescriptions dispensed nationwide. Considering that the average cost of a generic prescription is less than $30, while the average cost of a brand prescription is close to $95, it is easy to see how the Congressional Budget Office estimates the savings generated by generic drug use to be between $8 billion and $10 billion each and every year.

As this committee knows, Congress made these savings possible over 20 years ago with the 1984 enactment of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act. Hatch-Waxman achieves a critical balance between access to less costly generics and innovation of new brand-name drugs. I, and many others, believe that it is time for Congress to take the next step and let generic companies provide savings in the biological field. Doing so, however, will require brushing aside the current political maneuvering that threatens progress on this issue, and enacting appropriate legislation that would allow FDA to begin approving safe, effective, and affordable generic biologics.

DISCUSSION

Today, I want to briefly discuss three points that I hope this committee will consider as you move forward on generic biologics legislation:

- legislation must provide a regulatory pathway for approving generic biologics that is free of artificial barriers and unnecessary roadblocks, as well as a mechanism for allowing expeditious resolution of patent disputes that would delay generic market entry;
- market competition generated by generic biologics would unleash incentives for further innovation of newer medicines, just as Hatch-Waxman did over twenty years ago; and
- generic biologics will provide a market-based mechanism to help manage private and Federal expenditures and achieve significant savings.

I. LEGISLATIVE FRAMEWORK

Effective generic biologics legislation must include two parts: a regulatory pathway that allows FDA to expeditiously approve safe and affordable generic biologics and a mechanism for allowing generic companies to resolve certain patent disputes without delaying FDA approval. I will discuss some important aspect about both of these issues.

A. APPROVAL PATHWAY

Effective biologics legislation must include a regulatory approval pathway that does not impose unnecessary barriers to prompt market entry. Hatch-Waxman was largely successful in achieving this goal for generic drugs regulated under the Federal Food, Drug and Cosmetic Act, and this legislation should do the same for biologics regulated under the Public Health Service Act. An adequate abbreviated pathway must include, for example:

• clearly defined comparability criteria;
• provisions giving FDA discretion to require the needed tests—and only the needed tests—to make safety and effectiveness determinations;
• provisions setting forth the circumstances under which FDA can deny approval;
• provisions setting forth the contents of an abbreviated biological application;
• the ability to obtain an interchangeability rating that is immediately operative;
• no unique names for generic biologics, which is fully consistent with FDA's position that unique biologic names should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist;
• a timely review process that allows a company to discuss with the FDA research and testing and to know when action on the application can be anticipated; and
• an approval process that gives FDA flexibility as to what should be required on the label.

Equally as important, effective biologics legislation must not include provisions like those advocated by groups such as BIO—provisions that would unnecessarily delay approval and/or prevent consumers from receiving the biggest benefit from generic biological products. For example, legislation should not include:

• a requirement that all generic applications include full clinical and human trials, or any clinical trials other than those that FDA deems necessary to the relevant scientific issues;
• further legislation, or Congressional authorization/oversight or FDA regulations or guidances before the agency can give an interchangeability rating to a generic product;
• unique names for generic biologics, which would impede interchangeability findings and thus prevent the substitution of generic for brand that is essential for cost savings;
• provisions requiring agency-issued guidance or notice and comment rulemaking, which can take years and years to complete, before FDA can accept or approve a generic biologic application; and/or
• provisions requiring the generic company to have an identical label to the reference product, particularly where the brand has patented certain labeling information.

There is no justification for provisions like these, which will delay generic market entry and the interchangeability rating needed for consumers to benefit most from generic competition. They are entirely unnecessary to ensuring approval of safe and affordable generic biologics.

For example, while today clinical data may be needed for most biological products, Congress should not impose rigid requirements for such testing in all circumstances. Rather, Congress should give FDA the ability to draw on its decades of experience with these compounds by granting the agency the discretion to require such tests only when it determines that such clinical studies are needed.

It is significant that FDA agrees. FDA Deputy Commissioner Janet Woodcock addressed this during Congressman Waxman's Oversight & Government Reform Committee hearings last month, testifying that the "use of human subjects for trials that are not needed but are simply to check a box on a regulatory requirement is not desirable." Dr. Woodcock added that the ability to physically characterize protein molecules and other complex substances "has evolved and is continuing to evolve" and that "flexibility in enabling FDA to incorporate the new science into the regulatory process...is in the best interest of the public as well as the agency and the industry." Congress has entrusted FDA to make scientific judgments regarding drugs and biologics. This scientific advice from the agency should be headed.

Barr urges Congress to pass a regulatory framework for approving generic biologics that is free of unnecessary barriers and roadblocks in the form of artificial requirements, such as clinical studies and agency guidances. Such a framework will give FDA the flexibility it needs to approve safe and interchangeable generic biological products as quickly as possible.

B. PATENT PROVISIONS AND OTHER IP PROVISIONS

A key part of effective generic biologics legislation is a mechanism that allows the generic company to resolve certain patent disputes without that litigation impacting FDA approval. This was also a goal of Hatch-Waxman, although the brand industry has found ways around the law's intent, which was that patent disputes be resolved early, so that the generics can enter the market at the earliest time after valid and applicable patents have expired. Barr submits that any bill providing a pathway for generic biological products should take into account what we have learned from our 20-plus years of experience with the Hatch-Waxman patent provisions and improve upon that system in order to ensure that affordable biological products reach the public as quickly as possible. Thus, an effective generic biologic bill must, at the very least, contain patent provisions like the following:

• First, companies need patent certainty prior to marketing. Without it, companies will not invest in bringing affordable, comparable products to market prior to patent expiration because doing so could subject them to enormous patent infringement damages. Thus, effective legislation must include provisions that allow a generic company to obtain the required certainty—through litigation if necessary—while FDA is reviewing the application.

• Second, equally as important, however, is the fact that generic companies not be forced to litigate every patent relating to the brand product in order to obtain the patent certainty needed to launch. Thus, a biological patent system should provide a mechanism for litigating only those patent disputes that the generic company believes would delay its launch. There will be other patents—for example patents applicable to manufacturing processes that the generic company is not using—for which the only effect of early litigation would be unnecessary delay. I am not suggesting that the brand company should forever be foreclosed from asserting its patents. The brand company should have that opportunity, just not before the generic company markets its product. Accordingly, the system that will allow for the most expeditious generic market entry is one that permits the generic company to select the patents that will be litigated pre-product launch. This system also protects the brand company's intellectual property by allowing for suit on any patent that can reasonably be asserted after the generic company begins marketing.

• Third, generic companies need to be able to resolve patent disputes without those disputes delaying the FDA approval process, as we now experience with small molecule drugs under Hatch-Waxman.

• Fourth, generic companies must be able to litigate patent disputes quickly and efficiently. This will only happen if the generic company is permitted to designate a forum that would allow for more efficient litigation resolution. Right now, the brand company has the ability to bring suit against an ANDA applicant in virtually any district court in the country. Brand companies increasingly have brought suit in districts with the longest time to trial. In some courts, its takes from three to five years just to get to trial. Where certainty is essential, this means more delayed market entry.

• Fifth, if a brand company refuses to participate in the patent process, as increasingly happens with small molecule applications, the generic company must be allowed to enter the market without risking potentially massive damages. Under proposals such as those found in H.R. 1038, generic companies have some protection in the event that the brand company refuses to participate in the patent process. Brand companies have complained that this takes away substantive patent rights and forces them to give what amounts to a compulsory patent license. Not true. These provisions only apply if the brand company violates its statutory obligation to participate in the patent process. If the brand company follows the law, all of its patent rights would remain intact.

Finally, part of the so-called IP discussion surrounding generic biologics is the idea of exclusivity. On the generic side, the issue is clear: consumers and taxpayers, without question, will see the most significant savings from interchangeable products. Thus, it is essential that any generic biologics bill incentivize generic companies to do the work necessary to achieve an interchangeability rating from FDA. At present, no such incentive currently exists and, therefore, will need to be included in the legislation.

On the brand side, the issue also seems clear: lengthy, new exclusivity periods for brand companies are not necessary because the law currently provides more than enough incentive to continue innovating. For example, brand companies already get significant incentives, including multiple provisions allowing for patent term restorations, orphan drug exclusivity, and various tax credits. If the brand companies disagree, they are free to come forward and present data to support their argument. Indeed, Representative Waxman has invited discussion on this issue. However, the

brands have not yet come forward with any concrete data that would suggest that additional incentives are necessary. It is my view that only if they do come forward with such evidence should Congress consider enacting new exclusivity periods.

II. Generic Competition Will Spur Innovation

There is a misconception that market competition from generic biologics would diminish the incentive for originators to innovate new biologics. Generic competition will not slow innovation. In fact, just the opposite would be true. Market competition generated by generic biologics would accelerate further innovation of new biological products, while at the same time lowering the cost of treatment with existing medicines.

For example, Dr. Scott Gottlieb, recently the FDA Director of Medical Policy Development and Deputy Commissioner for Medical and Scientific Affairs, has explained: "Legislation to expose today's biologics to easier competition, after legitimate patents have expired, is going to accelerate development of improved products, not just lower-cost. Those making static assumptions .—.—. about how much savings this legislation is likely to bring are losing sight of the competition and progress it will have unleashed." [Forbes 4/17/07 edition (emphasis added)]. Similarly, the January 2007 study released by the Pharmaceutical Care Management Association concluded that increased competition from generic biologics would not only create pressure to reduce the cost of these products, but also produce added incentives for further innovation. Thus, generic biologics legislation would provide the dual benefit of increased savings and advancements in medical treatments.

III. Savings

No one can legitimately dispute that generic biologics will provide a market-based mechanism to help manage private and Federal expenditures and achieve significant savings. And no one can dispute that the American health care system has ever needed those savings more than it does today.

As the use of life-saving biological drugs continues to increase, so does the amount consumers and taxpayers spend. Indeed, spending on biotech drugs increased 21 percent in 2006, to approximately $40 billion, according to the 2006 Drug Trend Report. Spending in this sector is expected to grow to $100 billion over just the next four years. By 2010, biological medicines will account for 26 percent of total drug spending in the U.S. It is particularly important to note that Medicare spending for biological drugs continues to escalate disproportionately to Medicare funding. To put things in perspective, Medicare and Medicaid will spend $2.5 billion this year on just one biological drug—the anemia treatment Epogen—which is a half-billion dollars greater than the entire fiscal year 2007 budget of the Food and Drug Administration.

The solution to managing this spending is, of course, the use of safe and effective, lower-cost generic biologics. Just as generic chemical drugs have saved billions of dollars so, too, will generic biological drug products. A study released by Express Scripts in February 2007 showed that generic biologics would save payors $71 billion over 10 years. An Engel & Novitt study in January 2007, as well as other independent economic analyses we have seen, show that generic biologics would generate significant savings for Medicare Part B reimbursed medicines. Now, the brand companies take issue with some of these studies. Significantly, though, they do not take issue with the fact that generic biologics will save billions of dollars. They only take issue with how many billions will be saved. But in the end, whether the number is $71 billion or $7.1 billion, we simply cannot afford to lose the savings that, without question, would be achieved through use of generic biological medicines.

Congress should act now and pass legislation giving FDA authority to review abbreviated applications for generic biologics. The agency would be able to begin reviewing those applications as soon as they were submitted and the public would be assured that when the FDA approves a generic version of a biological product, just as has been the case with traditional drugs over the past 30 years, it will be safe, effective and have the same performance as the innovator product.

Chairman Palone and Members of the Committee, Barr always has been deeply committed to providing the public with affordable, safe generic drug products, and to do so as expeditiously as possible under the circumstances. That is why Barr has joined with consumer groups like AARP, Consumers Union, Families USA; employee unions life AFL-CIO and AFSCME; major corporations like Caterpillar, Ford, GM, and Kodak; healthcare providers Aetna, Blue Cross Blue Shield and Kaiser Permanente; pharmacy leaders like CVS/Caremark and the National Association of Chain Drug Stores; and no less than 18 of the nation's governors in calling on Con-

gress to pass legislation creating the framework for the approval of safe, effective and lower-cost generic biological drugs.

Congress has the opportunity this year to create—a huge win for patients, for taxpayers and for employers alike.— Indeed, effective generic biologics legislation very well could be the most important piece of consumer legislation enacted this year. We urge Congress to move forward in this effort.

Thank you, Mr. Chairman. I am happy to respond to any questions you and the committee may have.

Mr. PALLONE. Thank you. Ms. Hoffman.

STATEMENT OF RUTH HOFFMAN, EXECUTIVE DIRECTOR, THE CANDLELIGHTERS CHILDHOOD CANCER FOUNDATION

Ms. HOFFMAN. Chairman Pallone, Ranking Member Deal, and members of the committee, I sincerely thank you for giving me the opportunity to testify on an issue of great importance to the childhood cancer community and to me personally.

I am here today to explain the crucial role of biologics in the ongoing war on childhood cancers. Children with cancer have unique needs. They are not simply little adults; children have their own biological systems and unique tumor characterizations. Current toxic therapies that have proven effective for adults aren't a solution for children with cancer. In fact, these treatments are causing secondary cancers in the children who do survive to adulthood.

The best hope for children with cancer rests in the research and development of new and targeted biologics. So please don't deprive children with cancer future cures by depriving the biotech industry of incentives to innovate.

My name is Ruth Hoffman, and I am the executive director of the National office of Candlelighters Childhood Cancer Foundation. Candlelighters was founded in 1970 by concerned parents of children with cancer, and today we have a membership of over 50,000 families at the national office and more than 100,000 families across the country.

Advocating for children with cancer is my job, but I am also the mother of eight children, including a 20-year survivor of childhood cancer.

On July 10, 1987, my world changed forever. My 7-year-old daughter had been sick for 9 months. She had been diagnosed by her family physician as having a bug bite, a virus, an infection—she was on antibiotics; ear infections—she had tubes put in; tonsillitis, she had her tonsils and adenoids removed; and a neurotic mother, who is me. Despite these attempts to explain her failure to thrive, Naomi continued to deteriorate to a mere 32 pounds. So in shear desperation, I carried her to the emergency ward of our local Children's Hospital and it was on that day in July that I heard the words that seared my heart and my soul forever, my daughter had cancer.

Naomi was diagnosed with acute myelogenous leukemia, M5, the bad leukemia. Her prognosis was poor. Few survived AML in 1987. Fortunately, bone marrow transplants were just beginning as a potential therapy to treat children with AML, and her 9-year-old brother was a perfect donor match. Her treatment included IV chemotherapy for 5 days on, 24 hours a day, followed by 3 weeks off, and that continued for 5 months. This was followed by high-

dose chemotherapy and total body radiation. After 9 months of living in a complete bubble environment where for many months she never was able to get off her bed, Naomi was considered cured.

What I didn't know then but I sadly know now is that childhood cancer is for life. The 5-year survival rate used to determine adult cancers as "cured", has little meaning to children who complete treatment at 8 years of age. We are treating children with intensive toxic therapies at a time in their lives when they have growing bodies and developing brains. You can't treat a young child's body with these kinds of invasive therapies and not impact their overall health for the rest of their life.

Naomi did not emerge from her treatments unscathed, either. She has cataracts, heart damage, endocrine dysfunction, and is sterile. Then 2½ years ago, I received a second call that made my life stand still once again. Naomi was diagnosed with papillary thyroid carcinoma, metastatic to her lymph and bones, a second cancer but this was caused directly by the total body radiation that she received as a little girl to treat her first cancer.

Treatment for children with cancer really hasn't changed much since Naomi was originally diagnosed in 1987. Today all children with cancer continue to be treated solely, and I say solely with highly toxic cancer drugs that were developed 20 to 30 years ago. Only one new drug has received marketing approval by the FDA for childhood cancer in the last decade. That drug too was not a new class of smart drugs or biologics, it too was another toxic chemotherapy agent.

These traditional chemotherapy drugs have not provided a cure for many childhood cancer tumor types. Cancer remains the No. 1 disease killer of America's children, more children still die from cancer than cystic fibrosis, muscular dystrophy, asthma, and AIDS combined.

Those who do survive face lifelong late effects including severe drop in IQ, heart damage, sterility, deafness, severe growth deficits, and most shockingly, secondary cancers. What is even more disturbing is that these mortality rates have not changed in the last decade. I want to repeat that. Toxic chemotherapy and radiation treatments have not increased the survivorship of children within the last 10 years. We have reached a plateau with survival rates, and we have reached a limit of toxicity from current chemotherapy drugs and radiation treatments that we can give our children. I can't offer hope to any more families whose children are diagnosed with cancer today than I could 10 years ago.

Is there hope for these youngest cancer patients in this country? Absolutely. We stand at the threshold of a new era in the genetic treatment of disease. Large research initiatives are underway to identify the genetic fingerprints of many types of adult cancers, but funding for targeted therapeutic research for childhood cancer is minimal. What kids need is increased incentives for industry to develop new types of targeted therapies to treat children with cancer, not fewer incentives.

Children with cancer need treatment breakthroughs. They need new molecular-based therapies that will kill the cancer and not the kid. Biologic drugs have proven to be an effective weapon in the war on cancer for adults.

Today you are considering the important issue of allowing for abbreviated approvals of biosimilar products. We fully support increasing access to affordable drugs, but what kids with cancer really need most is access to drugs that can truly treat and truly cure their disease. Please don't create legislation that reduces costs by reducing incentives for biotech companies to develop targeted therapies for cancer. For me and for the parents I represent, lifesaving trumps cost saving any day.

My daughter Naomi draws her inspiration from something Ralph Waldo Emerson wrote: "Do not go where the path may lead, go instead where there is no path and leave a trail." We are a nation of trailblazers and innovators. I want to thank Representatives Inslee, Baldwin, and Green for introducing legislation that will enable this tradition of innovation to thrive in service to our Nation's children with cancer.

Candlelighters' motto is "...because kids can't fight cancer alone!" and I urge the members of this committee to think hard about the impact of your decisions on young lives. Kids can't fight cancer alone. They rely on adults like you and me to offer them hope so that they too may live a long a healthy life.

[The prepared statement of Ms. Hoffman follows:]

TESTIMONY OF RUTH HOFFMAN

Chairman Pallone, Ranking Member Deal, and members of the subcommittee, I sincerely thank you for giving me the opportunity to testify before you today on an issue of great importance to the childhood cancer community, and to me personally.

I'm referring to the crucial role of biologics in the ongoing war on childhood cancers. Children with cancer have unique needs. They are not simply "little adults;" children have their own biologic systems and unique tumor characterizations. Current toxic therapies that have proven effective for adults aren't a solution for kids with cancer—in fact, these treatments are causing secondary cancers in some of the children who survive to adulthood. The best hope for children with cancer rests in the research and development of new and targeted biologics. I am here today to explain to the committee how important it is that you not deprive children with cancer of future cures by depriving the biotech industry of incentives to innovate.

My name is Ruth Hoffman, and I am the executive director of the national office of Candlelighters Childhood Cancer Foundation. Candlelighters was founded in 1970 by concerned parents of children with cancer. Our mission, then and now, is to provide information and awareness for children and adolescents with cancer and their families, to advocate for their needs, and to support research so every child has the opportunity to survive and lead a long and healthy life. Today we have a membership of over 50,000 members of the national office and more than 100,000 members across the country linked to our 37 affiliate offices in 28 States.

Advocating for children with cancer is my job as Director of Candlelighters. But I am also the mother of a 20-year survivor of childhood cancer.

Twenty years ago, on July 10, 1987, my world changed forever. I was 31 years old, had a 9-year old son, a 7-year old daughter (Naomi), a 1-year old son—and I was 5 months pregnant with identical twin boys. My daughter Naomi had been sick for 9 months. She had been diagnosed by our family physician as having a bug bite, virus (put on antibiotics), ear infections (had tubes put in), tonsillitis (tonsils and adenoids removed), and a neurotic mother—me! Despite these attempts to explain her "failure to thrive," Naomi continued to deteriorate to a mere 32 pounds. She was no longer able to walk. So in sheer desperation, I carried her to the emergency ward of our local Children's hospital. It was on that day in July that I heard the words that seared my heart and my soul forever: "Your daughter has cancer."

Naomi was diagnosed with Acute Myelogenous Leukemia (M5)—the "bad" leukemia. Her prognosis was poor. Few survived AML in 1987. Fortunately, bone marrow transplants were just beginning as a potential therapy to treat children with AML, and her 9-year-old brother was a perfect donor match for Naomi. Her treatment included I.V. chemotherapy for 5 days on, 24 hours a day, followed by 3 weeks off, for 5 months. This was followed by high dose chemotherapy and total body radi-

ation. After 9 months of living in a complete bubble environment, Naomi was considered "cured.'

What I didn't know then, that I sadly know now, is that childhood cancer is for life. The 5-year survival rate used to determine adult cancers as "cured" has little meaning to children who complete treatment at 8 years of age. We are treating children with intensive toxic therapies at a time in their lives when they have growing bodies and developing brains. You can't treat a child's young body with these kinds of invasive therapies and not impact their overall health for the rest of their life.

Naomi did not emerge from her treatments unscathed. She had cataracts, heart damage, endocrine dysfunction, and was sterile. But she had her life, and she was determined to live it to the fullest. Then, 2½ years ago, shortly after Naomi graduated from college, I received the call that made my life stand still once again. Naomi was diagnosed with papillary thyroid carcinoma, metastatic to her lymph and bones—a second cancer—but this one was caused directly by the total body radiation that she received to treat her first cancer.

Naomi just keeps living her life and doing her best to invest it with meaning. She currently works at Children's National Medical Center here in Washington, DC, where she's employed as a clinical trial coordinator for a study of boys with Duchenne Muscular Dystrophy. She volunteers as a camp counselor for children with special needs including cancer, and she recently attended the Lance Armstrong Summit in Texas, where she represented and advocated for survivors of childhood cancer.

Naomi lives every day with the fact that, in all likelihood, cancer will end her life prematurely. But she hasn't given up hope. On the contrary, she's more committed than ever to making her life matter—not just to herself, but to other young people with cancer. She's so committed to the search for new molecular-based therapies for children with cancer that she is organizing her own fundraiser this November. Naomi's Hope for a Cure will raise money for research towards a genomic characterization of pediatric AML.

Treatment for children with cancer hasn't really changed much since Naomi was originally diagnosed in 1987. Today, ALL children with cancer continue to be treated solely with highly toxic cancer drugs that were developed 20 to 30 years ago. Only one new drug has received marketing approval by the FDA for childhood cancer in the last decade. That drug was not a new class of "smart drugs." It too was another toxic chemotherapy agent.

These traditional chemotherapy drugs have not provided a cure for many childhood cancer tumors, and they leave those children who do survive facing lifelong late-effects, including severe drop in IQ, heart damage, sterility, deafness and—most shockingly—secondary cancers. As a result, cancer remains the number one disease killer of America's children—more children still die from cancer than Cystic Fibrosis, Muscular Dystrophy, Asthma, and AIDS combined.

Every day I get calls from frantic parents around the country, looking for guidance and for hope. Just last week, I got a call from a young father whose 10-day old son, Jack, had just been diagnosed with a brain stem tumor. My job was to tell him that all doctors can offer infants like Jack is chemotherapy—they can't radiate children under three. What I did not want to tell him was that even with treatment there's only a 10 percent chance that Jack will survive to see his second birthday. Jack is not alone. Only half of children diagnosed with metastatic bone cancer will survive 5 years. Even today, half of children and teens diagnosed with Naomi's original cancer—acute myelogenous leukemia—will die within 5 years.

What is even more disheartening is that these mortality rates have not changed in the last decade! I want to repeat that: the toxic chemotherapy and radiation treatments that we are giving our children with cancer have NOT increased survivorship in the last 10 years! We have reached a plateau with survivorship rates, and we have reached the limit of toxicity for current chemotherapy drugs and radiation treatments. I can't offer any more hope to families whose children are diagnosed with cancer today, than I could 10 years ago.

As director of Candlelighters, I've come here to tell you that the status quo is not good enough for children with cancer. As Naomi's mother, I'm asking you: "Can't we do better for our children?"

Is there hope for this youngest cancer patients? The answer is a resounding YES! We stand at the threshold of a new era in the genetic treatment of cancer. Large research initiatives are underway to identify the genetic fingerprints of many types of adult cancers—but funding for targeted therapeutic research for childhood cancer is minimal, and lagging behind today's adult cancer research initiatives. What kids need is increased incentives for industry to develop new types of targeted therapies to treat children with cancer.

Children with cancer need treatment breakthroughs. They need new molecular-based therapies that will "kill the cancer, not the kid." Biologic drugs have proven to be an effective weapon in the war on cancer for adults, and one of the most promising treatments for the future. Because conventional chemotherapy and radiation treatments are so dangerous to children, young cancer patients are depending on innovative biotech companies to continue to develop more effective and targeted treatments in the future.

At this critical moment when targeted therapies are finally bearing the fruit of decades of research and providing new hope for cancer patients and their families, it is essential that we not undermine the development of these life-saving biologic agents.

Today you are considering the important issue of allowing for abbreviated approvals of biosimilar products. We fully support increasing access to affordable drugs. But what kids with cancer need most is access to drugs that can treat and cure their disease. A policy that produces more copies and less innovation will not help the children and their families living with cancer. Please don't create legislation that reduces costs by reducing incentives for biotech companies to develop targeted therapies for cancer. For me, and for the parents I represent, life-saving trumps cost-saving any day.

Elizabeth Edwards said in her statement to the press upon her relapse of breast cancer, "Femara didn't exist 5 years ago. I don't expect to get yesterday's medicine. If I can help it, I'd like to get tomorrow's medicine." Don't our children with cancer deserve the promise of tomorrow's drugs as well? The R&D pipeline for new biologics is a lifeline of hope for these kids and their families. Please don't shut it off.

My daughter Naomi draws her inspiration from something Ralph Waldo Emerson wrote: "Do not go where the path may lead, go instead where there is no path and leave a trail." We are a nation of trailblazers and innovators. I want to thank Representatives Inslee, Baldwin, and Green for introducing legislation that will enable this tradition of innovation to thrive in service to our Nation's children with cancer. And I want to thank the committee for recognizing that the future of biologics can't be measured in dollars and cents alone—that the bottom line for patients and their families is the priceless currency of life, health, and hope.

Candlelighters' motto is "... because kids can't fight cancer alone!" I urge the members of this committee to think hard about the impact of your decisions on young lives. Kids can't fight cancer alone. They rely on adults like you and me to offer them hope, towards a healthy adult future of their own.

Mr. PALLONE. Thank you, Ms. Hoffman, and thank you for telling the story about your daughter and implications that you think it has for the legislation. We appreciate it.

Dr. Weisbart.

STATEMENT OF ED WEISBART, M.D., CHIEF MEDICAL OFFICER, MEDICAL AFFAIRS, EXPRESS SCRIPTS, INC.

Dr. WEISBART. Thank you. First I want to just tell you how sorry I am for the problems in your family.

I am Dr. Ed Weisbart. I am the chief medical officer at Express Scripts, and I am a practicing physician; and I am delighted to be here today to talk about the issue of biogenerics from the perspective of a leading pharmacy benefit management company. Express Scripts would like to thank you and the committee for consideration of this historic policy which we believe will fundamentally improve health outcomes by giving people access to lower-cost biologic alternatives.

Express Scripts is one of the Nation's largest pharmacy benefit managers. We monitor prescription drug trends and expenses for 1,600 clients including large, self-insured nationwide employers; Government payers; unions; and across the sector health insurance companies, with over 50 million American lives. We work every day on behalf of our clients and their patients to make prescription drugs safer and more affordable. It should come as no surprise that

with the rise in cost of biotech pharmaceuticals that our clients are looking to us for advice on how to manage this ever-increasing biotech drug spend. In fact, our clients are demanding that we help deal with this issue.

I would like to make three main points today. First, specialty drug spending, especially in biologic agents, is growing at an alarming rate. Second, pharmacy benefit managers have developed many highly effective tools to manage the increasing cost of prescription drugs, and third, we are eager to apply these tools to biogenerics with the potential benefits to patients, plan sponsors, and the certainly to the Government.

Spending on pharmaceuticals is now 11 percent of total healthcare spending. Within pharmaceuticals are specialty drugs which are mostly the highly priced biologic agents we have been discussing. As spending for non-specialty pharmaceuticals now slowed to single-digit growth, specialty drug spending is now up to 26 percent increase in 2006.

In 2006, spending on specialty drugs was $54 billion, representing 20 percent of the pharmaceutical spending. In 2010, spending for specialty drugs will nearly double as we heard today to almost $100 billion. This rate of increase is the second highest rate of increase in healthcare today, exceeded only by diagnostic imaging tests, the second largest today.

As I said, Express Scripts represents 1,600 clients, managing the pharmacy benefit for over 50 million Americans. We have sophisticated tools such as formularies, tiered co-payments, step therapies, and a variety of other drug utilization management programs, just to name a few. These tools promote the most clinically sound and cost effective use of pharmaceuticals.

One of the most potent tools we have is the promotion of generic medications. Generic medications are time-tested, proven to be clinically effective, and have highly characterized safety profiles. An additional advantage, of course, is that they are the most affordable option for patients and plan sponsors. Because of the affordability and the other reasons, patients actually have higher compliance rates with generic medications than with the newer brand medications. Using these programs, our company leads the industry in filling as many as 60.3 percent of all prescriptions with generic drugs. If I had more time, I would be delighted to tell you of the success we have had lately in promoting the adoption of generics in the statin category last year. In that category alone, we saved over $230 million for our clients and their members, just since January 2006. Reducing costs safely, while preserving clinical outcomes and not shifting costs to patients is our core competency as a pharmacy benefit manager.

The money spent on biologics is increasing at an alarming rate. The legislation before you would allow for a pathway for FDA for companies to bring to market generic versions of these important medications. We have the tools today to assist patients in transitioning to these more cost-effective biogenerics. In fact, our transitioning tools would be even more effective in this market because of the limited number of patients involved, a limited number of prescriptions, and the limited number of treating physicians, not to mention the enormous potential savings. Our plan sponsors, our

clients, are extremely motivated to have us help pursue each and every one of these savings opportunities.

Regardless of whether the FDA deems a product interchangeable or comparable, we will be quite effective at working with prescribing physicians to help patients receive the most effective and clinically appropriate care. Many studies, including a detailed one by Express Scripts, have sought to demonstrate the potential savings associated with the FDA's ability to approve biogeneric products. They each differ in methodology assumptions but what is clear about each one of these studies is that the Federal Government as well as all payers stand to find savings in the billions of dollars. That is billions with a *B*, not a number you can ignore in healthcare today.

In closing, this historic legislation will allow patients, payers, physicians, and PBM's to work together to make these wonderful therapies more available with frankly improved health outcomes and tremendous savings.

Thank you for allowing us to talk about this.

[The prepared statement of Dr. Weisbart follows:]

TESTIMONY OF ED WEISBART, M.D.

Good Morning Chairman Pallone, Ranking Member Deal and other distinguished members of the committee.

I am Dr. Ed Weisbart, chief medical officer at Express Scripts, and I am pleased to be here today to discuss the issue of biogenerics from the perspective of a leading pharmacy benefit management company. Express Scripts would like to thank the Chairman and committee for their consideration of this historic policy issue which we believe will fundamentally improve health outcomes by giving patients access to lower-cost biologic alternatives.

Express Scripts is one of the Nation;s largest pharmacy benefit managers. We monitor prescription drug trends and expenditures for 1,600 clients including large, self-insured employers, government payers, unions and health insurance companies with over 50 million lives. We work every day on behalf of our clients and their patients to make prescription drugs safer and more affordable. It should come as no surprise given the dramatic rise in the cost of biotech pharmaceuticals that our clients look to us for advice on how to manage this ever-increasing biotech drug spend. In fact, they have been demanding action to make these therapies more affordable.

In my testimony today, I want to make three basic points:

- First, specialty drug spend, especially biologic agents, is growing at an alarming rate;
- Second, pharmacy benefit managers have developed many tools to manage the increasing cost of prescription drugs; and
- Third, how we would apply these tools to biogenerics and the potential benefit to patients, plan sponsors and the government.

I. Trends in Specialty Spend

Spending on pharmaceuticals now represents 11 percent of total health care spend. Within the pharmaceuticals are specialty drugs, which are mostly the high priced biologic agents being discussed today. As spend for non-specialty pharmaceuticals has slowed to single-digit growth, specialty drug spend increased 21 percent in 2006. [1]

In 2006, spending on specialty drugs was $54 Billion, representing 20 percent of the pharmaceutical spend. In 2010, spend for specialty drugs will almost double to $99 billion. This rate of increase is the second highest in health care field, exceeded only by diagnostic imaging tests.

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1 Express Scripts, Inc., 2006 Drug Trend Report, www.express-scripts.com/ourcompany/news/outcomesconference

II. Tools of PBMs

As I said, Express Scripts represents 1,600 clients, managing the pharmacy benefit for over 50 million individuals. To this end, we have developed sophisticated tools, such as formularies, tiered copayments, step therapies and drug utilization management programs to name a few. These tools promote the most clinically sound and cost effective use of pharmaceuticals.

One of the most potent tools we have is the promotion of generic medications. These therapies are time-tested, proven to be clinically effective, and have well characterized safety profiles. One additional key advantage is that they are the most affordable option for patients and plan sponsors. For these reasons, patients achieve higher compliance rates with these therapies. Utilizing these programs, our company leads the industry in filling as many as 60.3 percent of all prescriptions with generic drugs.

When a particular drug comes off patent and can be filled with a generic, that fill rate climbs to about 96 percent. An example of this would be when simvastatin came onto the market as a generic version of Zocor.

Where there is considerable patient monitoring needed, such as the case in preventing transplant rejections, what we call a narrow therapeutic index, physician prescribing patterns are more cautious and we see a generic fill rate of 83 percent.

These generic fill rates are based on empirical drug spend data.

It is important to recognize that all of our programs for promoting the use of generics, or less expensive branded medications, are reviewed by our external Pharmacy and Therapeutics committee. This independent self-governing committee is made up of both primary care and sub-specialty physicians and pharmacists, none of whom are employed by Express Scripts.

III. How We Would Apply PBM Tools to Biogenerics

As we have stated, the money spent on biologic agents is increasing at an alarming rate. This legislation will allow for a pathway at FDA for companies to bring to market generic versions of these important medications. PBMs have the tools to assist patients in transitioning to the more cost-effective biogenerics. In fact, our transitioning tools will be even more effective in this market because of the limited numbers of patients, prescriptions and treating physicians, and the potential enormous savings. Our plan sponsors will be very motivated to have us pursue each and every savings opportunity.

Regardless of whether the FDA deems a product as interchangeable or just comparable, we will be quite effective at working with the prescribing physician to aid patients in receive the most cost effective and clinically appropriate therapy.

To use a non-biologic example, Express Scripts' P&T Committee reviewed the potency of drugs called statins to determine the degree that they lowered LDL or "bad" cholesterol. Our independent P&T Committee concluded that three statins were in the "high-potency" category.

In this case, statin A had a much higher price than statin B. So, we educated consumers and physicians about the lower cost alternative brand product. We successfully moved 49 percent of market share to the preferred brand product within 6 months, and the outcomes for the patients are equally successful.

At the same time, statin B's product went generic. And, Express Scripts simultaneously moved 96 percent of market share to the preferred generic agent within 3 months, resulting in $230 million of savings since January of 2006 in the area of anti-cholesterol drugs alone.

While they have remained a relatively small percentage of prescriptions, biologics are the single, largest segment of drug spend, with an additional 400 to 700 biologics in the pipeline. The average cost per day of a biopharmaceutical is $45 compared with $2 per day for a traditional medicine. In the traditional drug market, generic medications decrease prices 60–90 percent as compared to branded oral-solid medications.

Many studies—including a detailed one by Express Scripts—have sought to demonstrate the potential savings associated with the FDA's ability to approve biogeneric products. What is clear about each of these studies is that the Federal Government—as well as all payors—stands to find savings in the billions of dollars.

In closing, this historic legislation will allow patients, payers, physicians and PBMs to work together to make these wonderful therapies more available, with improved health outcomes and tremendous savings.

Mr. Chairman and Members of the Committee, thank you for allowing me to testify before the Committee on this important issue. I would be happy to answer any questions you may have.

Mr. PALLONE. Thank you, Doctor. We will now go to questions from the members, and I will start. I am recognizing myself for 5 minutes.

I wanted to ask Mr. Kingham, as you heard, Dr. Woodcock—well, I don't know if you were here when she testified, presumably.

Mr. KINGHAM. Yes, I was.

Mr. PALLONE. She, at least I think she said, that clinical trials should not be mandated or required for the approval of follow-on biologics. She argued that FDA should have the flexibility to require different levels of testing depending on the complexity of the follow-on product and that while clinical trials might be required for the more complex molecules today, that could change with advancements in science. Now that seems to be at odds with your written testimony which states that clinical trials should be required for all products, and my question really is if the FDA is telling us that clinical trials shouldn't be mandated and we shouldn't have flexibility, why should we disregard that and require them? Aren't they the real experts that we should be listening to?

Mr. KINGHAM. Well, first of all, Congress has told FDA what to do with respect to the data to support applications for drugs on a number of occasions, so it is not unprecedented. And then the FDA has to do what you tell them to do. You did that in 1962 when you required proof of efficacy by only one type of clinical trial, not just clinical trials adequate and well-controlled clinical investigations. And in the legislation that Representative Waxman cosponsored in 1984 that Congress specified a particular type of comparative clinical trial, a bioequivalent study to demonstrate that generic drugs should be approvable.

So you have done it many times. But the fact is that at the present time, both in Europe and the United States, nobody has seen a protein product of the type that we are dealing with under section 351 that can be approved without some use in humans. I think as a matter of basic science and policy, it is entirely reasonable to require some experimentation, some clinical use of a product before it is introduced into medical practice in those circumstances. I am quite happy that the FDA has substantial discretion as to the exact testing that is required. Right now where they have that discretion they are requiring substantial clinical tests, not minor ones but major clinical tests lasting months and involving substantial numbers of patients.

Mr. PALLONE. So you think there should at least be some trials, it is just a question of what they would do?

You give flexibility in what they do but——

Mr. KINGHAM. I think the thing that disturbs me in at least one of the bills that is before this committee, H.R. 1038, is that while the legislation does ultimately give the FDA the power to require a clinical trial, it segregates the clinical trial issue from other types of data and attaches to it a sort of warning to the agency that they better not require duplicative or unethical tests. Now, I have never seen anything like that in a bill directed to the FDA before, but the message that it clearly sends is you shouldn't really be doing this. The message I heard from Dr. Woodcock was most of the time, probably all the time for the foreseeable future, for the types of

proteins that are regulated under section 351, some form of clinical testing is going to be necessary.

Mr. PALLONE. I will admit that it wasn't totally clear what she was saying. I would like to ask Dr. Allan. When Hatch-Waxman was enacted in 1984, his detractors claimed that it would stifle innovation, yet the number of new technologies developed in the last 20 years, particularly in biologics, has been staggering. You noted in your testimony that the pending legislation would be a positive step for the biotech industry and would continue to fuel the cycle of innovation. You want to just elaborate on that a little if you could? Now, I am talking about Mr. Waxman's legislation.

Mr. ALLAN. Yes. I think the innovation that would be stimulated by an act of this type would be enormous in the area of analytical methodology to characterize proteins, there would be an absolute rush to the door for people to develop this methodology, to assist in the development of these novel protein products. We were hearing this morning that science might be many years away. I would absolutely guarantee that if the incentive was provided to the scientists out there in both research laboratories within universities or biotech companies that there would be an enormous leap in our knowledge of how to characterize proteins efficiently and effectively.

Mr. PALLONE. OK.

Mr. ALLAN. And this argument would disappear.

Mr. PALLONE. OK. Thank you. Ms. Hoffman, I appreciate your being here and what you said. But the way I see it, innovators have a virtual monopoly on the market now and aren't necessarily doing the research and development that you say is needed. So I guess what I don't understand is how the approval of the follow-ons which we are talking about today would dramatically change the playing field. In other words, if we approve a pathway for follow-ons, then why would that mean that there would be any less innovation along the lines of what you suggest or what you think is needed?

Ms. HOFFMAN. I guess I was saying that in terms of orphan diseases—diseases like childhood cancer, it doesn't appear that there is enough incentive to be producing biologics and new treatments and new therapies for these patient populations; and I can't see that by reducing any sort of incentive that that is going to make things better.

So my proposal is that anything to cut back on incentives is going to make things even worse. I mean, we are already at zero, but we have no hope, none at all, to even get on the playing field. And I mean, it is not just childhood cancer, it is all orphan diseases, whether it is muscular dystrophy or other children's diseases, it is a huge issue. And if we take that incentive away from biotech companies, I just don't see that there will be cures that come down.

Mr. PALLONE. I understand your concern. You want to make sure that we don't eliminate incentives.

Ms. HOFFMAN. Yes.

Mr. PALLONE. Thank you. Mr. Deal.

Mr. DEAL. Thank you. I want to thank all the witnesses. You have been very helpful, very informative and your written testi-

mony elaborates even further than your 5 minutes did. I thank you for that.

Mr. Kingham, let me ask you specifically some questions so I can clarify some terms here and thank you for refining your testimony down to talking about the issue of exclusivity. I do believe that is one of the two, in my opinion, major areas. The other big major area I would classify would be the overall safety issue, and I want to talk to some of you about that in just a second.

Let me first of all understand: patent extension currently extends to biologics, does it not?

Mr. KINGHAM. Yes, it does, sir.

Mr. DEAL. OK. In your literature and in your attachment in particular, the terms market exclusivity and data exclusivity are used. Are they the same information? Is it the same term? Does it mean the same thing?

Mr. KINGHAM. No, not necessarily. Market exclusivity is a term for a period during which there is not competition because of some regulatory or other legal protection. It can be a patent, it could be orphan exclusivity under the orphan drug amendments, something like that. Data exclusivity is the period during which someone cannot rely upon your data to get a follow-on product approved. Data exclusivity does not preclude another company that is prepared to do research and development and do its own clinical trials from obtaining approval of a competitive product. That is why we have multiple biologic products in a number of therapeutic categories today because different companies did the work to support their products.

Mr. DEAL. So when you were talking about the 14 years, you were talking about market——

Mr. KINGHAM. That is correct. What I am saying is that I believe Congress made a judgment in 1984 that that was a reasonable period to provide the incentives needed to do the research and development.

Mr. DEAL. OK. Now, in terms of data EE, that comes to the issue of how much can a follow-on piggyback onto what FDA currently has submitted by the original innovator, am I correct?

Mr. KINGHAM. That is correct.

Mr. DEAL. All right. Are you advocating a period of data EE?

Mr. KINGHAM. Yes, I am.

Mr. DEAL. How long?

Mr. KINGHAM. Of 14 years and the reason for that is that I believe that with all the various problems I identified, we cannot be sure that patents will provide a certain period of market EE. I would propose that that be provided with data EE.

Mr. DEAL. If we are talking about market exclusivity being different than patent protection which I understood you to advocate, why would you also need data EE?

Mr. KINGHAM. You need it because the patents may not protect the products under a system of——

Mr. DEAL. But if you got a statutory market EE, that gives you the protection, does it not?

Mr. KINGHAM. Yes, sir, if the provision of the law were similar, for example, to what is in the orphan drug amendments of 1983 which provides a period of time during which a competitive product

cannot be approved without regard to patents, without regard to data and so forth. That would achieve the same purpose.

Mr. DEAL. OK. The data exclusivity to me comes under my big category of the safety issue as to how much can you use in determining the safety of the follow-on product. In that regard, I have been intrigued by some indications of people who suggested that we look at the FRFRA provisions of the EPA as it relates to the regulation of pesticides. They have some unique statutory provisions there. Have you had any occasion to ever look at those?

Mr. KINGHAM. Well, I have. Of course, the pesticide law led to some very serious constitutional problems back in the 1970's when the Environmental Protection Agency under instructions from Congress sought to use the data that had been submitted by innovators in order to approve follow-on pesticide products, but they had actually assured people who filed data under the previous application system that the data would not be used in that manner. That led to a significant constitutional issue and very complicated questions concerning how and if to compensate people for the use of their data which brought down the whole registration system for a number of years.

Mr. DEAL. My reading of the Ruckelshaus case in 1984 that was supplemented by the *Thomas* v. *Union Carbide* case of 1985 seems to have approved at the Supreme Court level those statutory schemes, and in that regard I need to ask you this question before time runs out.

Mr. KINGHAM. OK.

Mr. DEAL. Part of that was all based on I think what the language was, reasonable investment backed expectation that the information submitted to a Government agency would not be violated or remain invalid.

Mr. KINGHAM. That is correct.

Mr. DEAL. Is there anything as you see it under current law that gives to current innovators of biologics a reasonable investment-backed expectation that the information would not be shared? If so, is it stated or is it simply implied?

Mr. KINGHAM. Well, in 1974, the Food and Drug Administration said in the Federal Register that they would not use the safety and effectiveness data filed under an application under section 351 of the Public Health Service Act to approve competitive products. It was very clearly stated that they would not approve generic products on the basis of data that were submitted by innovators.

Mr. DEAL. Other than that, is there anything that you think is there?

Mr. KINGHAM. Well, that has been the continuous course of conduct since then. The agency has never taken that back, and the regulation that it promulgated on the basis of that legal approach remains in effect today. It is a bit complicated because it has to do with the implementation of the Freedom of Information Act, but the representation has existed since 1974 that data will not be used to approve other people's products.

Mr. DEAL. Thank you.

Mr. PALLONE. Mr. Waxman?

Mr. WAXMAN. Mr. Chairman, with all due respect, Mr. Kingham is a lawyer and he is presenting to us his understanding of the law,

but perhaps we ought to have lawyers from the generic industry as well. I certainly can't substitute for them, but I can tell you I wrote these laws. And I think that the gentleman has made some statements that are incorrect.

There is a patent, and the patent is for 20 years. When you go into FDA, there is a period of time in which FDA takes to review it. Sometimes there is a delay at FDA because of FDA, sometimes there is a delay at FDA because of the manufacturers. The argument in the mid-1980's was in addition to the patent, there ought to be exclusivity for some of the time lost at FDA for approval. So the bill is the restoration of some of that time. The law didn't guarantee 14 years, it said up to 14 years. That was the maximum. Now, what we have presented to us from the industry, the bio industries, they ought to have a minimum of 14 years.

Now, we also provided some other exclusivities. We provided exclusivity of only 5 years for the most innovative new molecular entity, because we wanted to encourage the companies to look for new uses for some of the drugs that were out there, and we said we will give you 5 years of exclusivity. Well, that was 5 years for something really worthwhile. If it weren't so dramatic, we gave them 3 years.

I also wrote the Orphan Drug Act. The Orphan Drug Act was to give an incentive to develop drugs that weren't profitable, so we provided a term of exclusivity in the Orphan Drug Act. Now we have the testimony from Mr. Kingham that we ought to give them what was given under the Orphan Drug Act, but these are companies that are making biological drugs that are profitable. Nobody is going to want to make, by the way, a generic version of a nonprofitable biologic drug. So the question then should be should they have the same kind of exclusivity that was given to the orphan drug act which was to make up for the fact that they probably weren't going to get a big windfall. By the way, many of them did. You can never take back exclusivity. You can never take back some of that period of time.

So if I were looking for the wish list of the biotech industry, since they now take the position, well, we ought to have a pathway, my wish list would be as follows. Let us give the companies that are already on the market and may be on the market with new products as much exclusivity as possible, and that is certainly what they are arguing. It is in their economic interest to argue for that position. I would also argue, Mr. Schwieterman, if I were in the biotech industry that argues that any legislation should rule out the possibility of establishing interchangeability because "it is not possible in the present state of science and technology to treat them as interchangeable." Do you agree that it is impossible given the current state of science to devise studies necessary to determine whether two biologics are interchangeable?

Mr. SCHWIETERMAN. No, I don't agree. I don't agree that it is impossible. The use of the term interchangeability is a term that connotes confidence in data and the science and the use of a product in a particular patient that provides a particular effect. It is to me a term that actually is science-driven and data-driven, and I think it fully possible in certain settings where the data exists and in the

context of the application an indication that you could, in fact, in those——

Mr. WAXMAN. In fact, the terms in my bill is lack of significant clinical difference in the safety of effectiveness. So in effect, you can have an interchangeable provision. Well, if I were I guess from the bio industry, I would say, well, I certainly don't want this to be considered equivalent in this way because it will be substituted. That is how we get our big savings is we substitute a generic drug.

Mr. Downey, a number of proposals would require FDA issue guidance to classic cases of biologics before the agency may approve a generic biologic. You have experience with the agency both as a generic manufacturer and as a company that sells some brand-name products. Would requiring a guidance for a class of generic biologics be consistent with current FDA policy and would it make sense?

Mr. DOWNEY. Well, no, it is not consistent with FDA policy today. Even the innovative biologic products are not subject to a guidance. They propose their own product and their own guidelines, and the FDA comments. That is precisely what happens in BLA's, new drug applications, abbreviated drug applications, and that is what we think should happen here.

Mr. WAXMAN. Well, if I were from BIO and I was trying to figure out how do I extend my exclusivity period, I would also want to complicate things by several years making me have to go through this rigmarole.

Mr. DOWNEY. I believe if we had that process the first generic biological would extend beyond the career horizon of the current executives in the bio industry.

Mr. WAXMAN. Then you make them do more clinical trials. That also would postpone the competition. So you want more exclusivity and if that doesn't protect you to make maximum profits, then you want more obstacles before you get the competitor out there.

All of the wish list is in the other bill that is before this committee. I think we all agree there ought to be a pathway and there needs to be a balance. But we need incentives not only for new products, we need incentives for generic products as well; and before the Hatch-Waxman Act was adopted over 20 years ago, there was no generic industry. In fact, the only thing the generic guys did was reproduce the drugs for the brand-name companies. The brand-name companies said, well, they don't know how to do this sort of thing. Well, they were actually making the drugs but the brand-name companies were selling them for whatever the monopoly would allow.

We want that balance for both sides, and I would submit that the bill that Mr. Inslee introduced is one that I would want us to walk through very carefully and make sure that that balance is achieved.

Thank you for that.

Mr. PALLONE. Thank you. Dr. Burgess.

Mr. BURGESS. Thank you, and thank you all for being with us. It really has been an informative panel.

Dr. Schenkein, if I could ask you, you heard the line of questioning that Mr. Waxman was just following. Is that period of EE, is

that something that you feel is important to the continued development of breakthrough and innovative products?

Dr. SCHENKEIN. I do. I believe it is critically important. As we look at the development of biologics, particularly as they have a better efficacy-to-safety ratio, they are safer, they appear to be more effective, we move them into the agavent setting. By doing so, we need to wait for the pivotal studies to first be done in the metastatic setting. So the timing by which we can move these medicines up to the agavent setting where we believe they will have the biggest impact and potential possible cures, particularly in malignancies, and transform other illnesses, takes a long period of time. It can be as long as a decade after the original approval to complete or design those studies.

Mr. BURGESS. Let me see if I understand that concept correctly. You are developing these products that are used in individuals with fairly advanced disease, stage IV metastatic cancer, and as you develop the expertise of the comfort level with those products, they are then possibly going to be investigated as agavent therapy for someone with early stage disease to prevent recurrents and extend life at an earlier stage of a similar cancer, is that——

Dr. SCHENKEIN. That is absolutely correct, and that period takes a long period of time.

Mr. BURGESS. Is it possible to make some of these difficult compounds, is it possible to make them so that they are just absolutely identical? We heard the testimony from the gentleman from Express Scripts about the symptostatin story and no doubt that someone can make an exact replica of that molecule, with some of the things that you work with, is it going to be possible to make an exact replica of the molecule?

Dr. SCHENKEIN. At this point the science that we have available today, it is not possible for us to say that these are the same.

Mr. BURGESS. How do you even then extrapolate that to the individuals where we are going to treat their lymphocytes and give them back those? I mean, how do you do a study when your population is one and it is either effective or it is not?

Dr. SCHENKEIN. That raises the complexity even to the next level above the standard proteins or antibodies that are being processed now. So it will become even more complicated than that setting.

Mr. BURGESS. But as we get into the realm of personalized medicine of individuals, that is going to be critical, is it not?

Dr. SCHENKEIN. I believe so.

Mr. BURGESS. And it will be expensive, will it not?

Dr. SCHENKEIN. It is too early yet. We don't know. We know that these innovative——

Mr. BURGESS. Let me rephrase that. Even if it is expensive, it is very likely to be worth it, is that a fair statement?

Dr. SCHENKEIN. After careful testing, if it determines safety and efficacy, then that will be a therapy that will be useful.

Mr. BURGESS. What about the doctor who writes a prescription for someone to go to the drug store and fill it with recombinant DNA—in your experience would it be OK for someone just to substitute something different from what the doctor has established as the product that he wants his patient to receive?

Dr. SCHENKEIN. As a physician, I think it is critically important that I have that relationship with my patients so I know exactly what that patient is receiving when I prescribe it. I am making challenging decisions at every point about a variety of different medicines I can use. And unless the product is exactly the same, which we are not talking about in the case of follow-on biologics, I need to have the ability to make a decision with that patient on which medicine I want to give them.

Mr. BURGESS. Is that a big enough difference to be a difference? Could that affect the critical outcome of a patient?

Dr. SCHENKEIN. It is certainly possible. When I make a decision to use a therapy, I base that decision on clinical evidence, large-scale clinical trials that have been published and presented. If that is not available for another molecule, I factor that in the decision. It is a totally different level of evidence to be able to base an important decision with a patient.

Mr. BURGESS. If I could, I would like to ask a question. I would like both you and Mr. Kingham to respond and anyone else if you feel so moved. When I first heard of this issue of generic biologics or follow-on biologics, I thought that has to be a pretty small universe. We talk of savings, again the gentleman from Express Scripts talked about with statins. That is a huge universe. But when we talk about follow-on biologics, and maybe it is just an era that is just beginning, but realistically, what kind of savings can we expect, should we expect if we were to pass say the Waxman bill through Congress this year?

Dr. SCHENKEIN. So again, as a physician and an oncologist designing clinical trials, I don't think that is my best area of expertise to comment on cost savings.

Mr. BURGESS. Well, then Mr. Kingham, do you have an opinion about——

Mr. KINGHAM. Well, I can't give you a precise number but I think there are a number of reasons why the number will be smaller than many advocates of the legislation suggested. Studies that I have seen assume that there aren't any effective patents for any major products where as there are. They assume that the legislation and regime would be in place immediately and drugs would be improved within months or a very short period of time after the law was passed. The European experience doesn't support that. They have had a system in place for 3½ years and they have approved two products.

It assumes that a number of products that present very complex issues for approval, like monoclonal antibodies and so forth, would be in the groups of products that will get approved and will compete. I think it is going to be a long time before the science is there, much less the patent situation. It assumes tradition or something very similar to traditional substitution patterns for generic drugs.

Quite apart from the scientific issues of interchange, these drugs aren't administered and dispensed in the same way so that the patterns of substitution that apply with prescriptions taken to the drugs store won't be relevant. And it assumes price differentials that I think may be greater than the price differentials that will actually occur based on experience in markets outside the United States. There are a lot of assumptions that have been set into these

projections. I suspect we are talking about savings, and there would be some for sure that are a small fraction of the savings that have been suggested.

Mr. BURGESS. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Dr. Burgess.

Mr. DOWNEY. I would like to respond to——

Mr. PALLONE. OK. But let me just tell everybody what we are going to do here. We have to vote on the Iraq supplemental, and we only have 13 minutes. So we will ask Mr. Downey to respond, and then we are going to have Ms. DeGette and then we will go and vote.

Mr. DOWNEY. There is only one aspect to Mr. Kingham's response that I agree with and that is there will be very few approvals in the first 5 years because it takes a longer time to bring the generic versions to market than a generic pharmaceutical. But today, the Taxpayers Against Government Waste issued a report where they said after the first 5-year period, the next 10 years will result in $43 billion in savings and I don't think that is an unreasonable estimate. And I do strongly disagree we won't achieve the same substitution rates. I know that we believe that we achieve those rates in the hospital setting for other pharmaceutical products, we will achieve them here. I know that the drug benefit managers like Express Scripts do an excellent job of educating patients and physicians about the benefits of generic products, and I am sure they will carry that expertise into the biologic areas and we will achieve those substitution rates and we will achieve that level of savings.

Mr. PALLONE. Thank you. The gentlewoman from——

Dr. WEISBART. May I?

Mr. PALLONE. Well, I just don't want to run out of time. If you want to be quick, go ahead.

Dr. WEISBART. I will be very brief. A couple quick points. Your decisions will determine how much the savings is. Your decisions will determine that. If you decide to follow some of those recommendations, you will have very little savings. If you decide to pay attention to the wisdom of Mr. Waxman and yourself just a minute ago, your savings are potentially enormous. Clients are pressing us to do this. They are not that many prescriptions, they are all handled through specialized pharmacists with a few physicians we know how to reach them. If you think of the savings I just talked about for Simvastatin for a $40 or $80 change of prescription, these are hundreds of dollars. Our clients are very motivated to have us do everything we are doing today and way more to make these savings happen. In terms of the timing of this, that is up to the courts. As we know, there are lots of drugs that come off patent protection for which generic drugs reach market years in advance of when the brand manufacturers—but the 10K filing would make you think that is the not case.

And last, a large part of the savings early on are due to erythroproteins which a large percentage of it comes to the Federal Government. So the savings that are potential here are savings for the Federal Government in large part. It is a huge opportunity. That is soon if you introduce legislation.

Mr. PALLONE. All right. Thank you. I recognize the gentlewoman from Colorado for 5 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman. I am a little nervous because I do want to vote on the supplemental.

Mr. PALLONE. You have 11 minutes left. If you take 5 we will still get there.

Ms. DEGETTE. I want to ask you, Dr. Shenkein, as we have been hearing this testimony, the view of all of the representatives at BIO who are here is that because biologics are so complex, it would be very difficult to create a generic version; and what we have heard from several of the witnesses is BIO seems to be supportive, employing a biosimilar pathway similar to the one in the EU which relies heavily on clinical trials. So if that is the case, do you think we will ever have a situation where biosimilar will not have to go through pretty much full clinical trials before approval?

Dr. SCHENKEIN. I can't obviously predict what will happen in the future. All I know is right now, the science in the foreseeable future, we don't have the ability to be able to determine that these molecules are the same.

Ms. DEGETTE. So your answer would be in all probability these follow-on biologics would need to go through a full clinical trial, correct?

Dr. SCHENKEIN. Yes.

Ms. DEGETTE. Well, then my next question, and I am going to also ask Mr. Downey that question, too, is we have several proposals in front of us to create these pathways to approve follow-on biologics, and I haven't signed on to any of these approaches because like most of us, I am still trying to figure out the right balance. But all of the approaches are predicated on the belief that the FDA is going to handle increased responsibilities for the process. So my question is given the fact the FDA is continuing to struggle to meet its current obligations with fewer and fewer resources, what would that agency need to be able to oversee a whole new pathway for biosimilars? I want to start with Dr. Schenkein, and then I want you to answer.

Dr. SCHENKEIN. So we do believe it is critically important that with any policy that moves forward that it doesn't distract the FDA from the ability to review and approve innovative drugs that are advancing the field forward. That has to be the primary focus. I can't comment on what the FDA would require to be able to——

Ms. DEGETTE. Do you think they would need substantial additional resources to do this job adequately?

Dr. SCHENKEIN. I can't really comment.

Ms. DEGETTE. OK. What about you then Mr. Downey?

Mr. DOWNEY. House bill 1038 provides user fees to support the generic biologic program at FDA and——

Ms. DEGETTE. Some of us have real concerns about user fees, too.

Mr. DOWNEY. Well, you asked how it would be funded.

Ms. DEGETTE. OK.

Mr. DOWNEY. At least in 1038 it contemplates user fees, and I would support that because I think the FDA does need additional resources and that is a place from which they can come and there will be great savings achieved by it. On the clinical trials, I disagree with the comments that were made. In terms of mandating clinical trials in the statute, that is not required for an original innovator BLA. Those requirements are all imposed by FDA on a

product-by-product basis with product relevant clinical testing. That is handled in the drug area, it is handled in the innovator biologic area, and what we believe is appropriate for generic biologics. And I think also if you recall Dr. Woodcock's testimony, she said they have approved products with limited clinical studies and those that have required more clinical studies.

Ms. DEGETTE. But all of them needed clinical studies.

Mr. DOWNEY. For today.

Ms. DEGETTE. So I think for today we have to go on that assumption.

Mr. DOWNEY. I would disagree. I think you need to think as I talked about it earlier, it is 20-year cycles. This is the bill that I think will last 20 years, and as you all know it is very difficult to reopen these very contentious and difficult issues; so I believe we should provide FDA the flexibility and the resources to handle this issue for a long period of time. And if you look at the products, I do disagree with some of the testimony here today. I think simple proteins, like insulin, can be fully characterized and they don't really require the clinical trials. Now, I realize that FDA is probably going to disagree with me on that, but I do believe that science is advancing so fast and it is so clear that in a very short time we will be able to have very minor clinical trials, if any.

Ms. DEGETTE. I will say, I don't disagree with what you are saying, but I do think it is probably a little naive to say we will just do user fees and that will cover the cost. I am really going to look forward to working with Mr. Waxman and Mr. Pallone to make sure that whatever we do here, we give the FDA adequate resources to do this. I myself have a 13-year-old daughter who is insulin-dependent. I am not going to use a generic insulin with her unless I am pretty darn well sure. Ms. Hoffman, mother of eight, is sitting here nodding, too. We are just not going to do that unless we are sure.

Mr. PALLONE. I am going to have to stop you. I appreciate it because we want Mr. Inslee to have a little time, but there is only 5 minutes left on the vote. You are at your own peril here. You might have missed the vote.

Mr. INSLEE. Regarding data exclusivity we have a couple of numbers that have been suggested so far, one is zero and one is 14 years. And the previous incarnation which I appreciate Mr. Downey, he called it the Waxman-Hatch bill. That is appropriately honoring the House.

Mr. DOWNEY. I try to remember which house I am in.

Mr. INSLEE. I appreciate that. It had between a 5- and 14-year data exclusivity as opposed to paying—is there any reason that any of you could articulate to go backwards to zero on that if indeed there was a societal purpose to protect data exclusivity for the reasons Mrs. Hoffman has talked about, to have an incentive for innovation. Is there any reason to have gone backwards? For instance, is it easier to do a follow-on biologic for instance and some of the other chemical or is the FDA much faster than it used to be so that you don't need that much protection? Is there any reason to go backwards to zero? Can anyone articulate any reason?

Mr. PALLONE. Let me just indicate we are going to have about a minute to answer the question and then we got to go because otherwise we are going to miss the vote.

Mr. KINGHAM. Well, I would just say quite simply no, I can't conceive of any reason for a zero.

Mr. INSLEE. That is the right answer. I have to go vote. Thank you very much.

Mr. PALLONE. Thank you. Thank you, gentlemen and lady. We appreciate your input. This was a very good hearing I feel, and I got a lot of insight. It is a very difficult and complex problem, so we thank you very much. You may get additional questions in writing from us within the next 10 days which we would like you to respond to, and without further ado, this hearing is adjourned.

[Whereupon, at 2:30 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

STATEMENT OF PRIYA MATHUR, CALIFORNIA PUBLIC EMPLOYEES' RETIREMENT SYSTEM

On behalf of the California Public Employees' Retirement System (CalPERS), I appreciate the opportunity to provide testimony for the hearing record on the high cost of biopharmaceuticals and the need to establish a safe pathway for the approval of biogenerics. As vice-chair of Health Benefits for the Board of Administration of CalPERS, I was elected by 400 thousand public sector members to serve on the board of CalPERS to invest their $230 billion of retirement assets and to manage their multi-billion dollar health benefit program.

The high cost of biopharmaceutical products presents an unsustainable challenge to CalPERS and to our entire health care system. At a time when our state is trying to expand health insurance coverage to more Californians, slow the rate of growth in health care costs, and make our health care system more efficient, we cannot afford the status quo. I commend Chairman Pallone for his leadership in this area. In addition, I would like to thank the sponsors of the bipartisan Access to Life-Saving Medicines Act, introduced by Representatives Waxman, Emerson, Pallone and others.

CALPERS BACKGROUND

CalPERS was established by state law in 1932 to provide retirement benefits for California public sector employees. In 1962, state law authorized CalPERS to provide health benefits to their members. Our mission is to advance the financial and health security for all who participate in the System.

CalPERS' health program covers 1.2 million active and retired state and local government public employees and their family members. Of that total, approximately two-thirds are active members and one-third are retirees. Notably, CalPERS is the third largest purchaser of employee health benefits in the Nation—behind the Federal Government and General Motors Corporation—and is the largest purchaser of health benefits in California.

This year, CalPERS will spend almost $5 billion on health benefits—or $13.4 million per day. Of that amount, CalPERS—for the first time—will spend over $1 billion on our members' prescription drugs.

SLOWING THE RATE OF GROWTH IN HEALTH CARE

Recognizing that we have a fiduciary responsibility to constrain cost growth and ensure healthcare value, CalPERS has long been a leader in implementing cost-effective programs. These initiatives include consumer-friendly managed care, aggressively negotiating favorable contracts with insurers by leveraging our pool of enrollees, state of the art hospital purchasing and quality assurance arrangements. In addition, we have instituted innovative prescription drug benefit cost-sharing designs to maximize the use of generics and therapeutically appropriate brand drugs. We have also provided incentives for the use of over-the-counter and mail-order medications and mail-order, particularly for the treatment of chronic diseases.

CalPERS has enjoyed tremendous success in controlling prescription drug costs through the use of generics. This has been possible thanks to the efforts of this

Committee, and particularly Mr. Waxman, whose efforts two decades ago led to the enactment of the "Drug Price Competition and Patent Term Restoration Act of 1984," better known as Hatch-Waxman.

As members of this committee well know, Hatch-Waxman gave the Food and Drug Administration (FDA) the authority to provide an abbreviated approval process for those products deemed equivalent to an innovator product once a product's patent had expired. For multi-source drugs in our self-funded PPO, which covers about a quarter of our members, our generic substitution rate is approximately 96 percent. Without generic substitution, we estimate that our costs would be about 60 percent higher—saving our enrollees and our state taxpayers hundreds of million of dollars annually.

In spite of all of our cost-containment efforts, we are experiencing double-digit increases in health care spending over time. Since 2002, CalPERS has seen an average annual increase of about 13.5 percent for our HMOs and PPOs, and a 12 percent average annual increase in our association member plans.

INCREASING COST OF BIOPHARMACEUTICALS

Because of the complex delivery requirements of many biopharmaceuticals, it is exceedingly difficult to break out a stand-alone spending line for these products. However, we believe that our spending on so-called "specialty drugs" is a good proxy because biotech products make up the great majority of spending in this category. CalPERS spending for these products is distressingly substantial and rising at a rate that is significantly higher than traditional pharmaceuticals.

Total spending for specialty drugs was $83.7 million in 2006, up from $67.4 million in 2004. Spending on these prescriptions increased by 16.9 percent in 2005—compared to a 5.4 percent increase in traditional prescription drugs. On average, spending for biotech products was at least $55 per day—compared to traditional drugs at only $2 per day.

PROMISE OF BIOGENERICS—COMPETITION AND LOWER COST

CalPERS supports a competitive health care marketplace that leads to innovation and further development life-saving medicines. Today, biopharmaceutical manufacturers enjoy monopoly positions. Today, unlike traditional pharmaceuticals, no competition is created in the marketplace once a patent has expired on a brand name biopharmaceutical. Competition does not exist because the FDA has held that it does not have the authority to approve biogeneric products. CalPERS supports giving the FDA explicit authority to approve biogeneric products that are safe.

It is imperative that Congress take action this year to enact bipartisan legislation to give FDA the authority to approve safe biogenerics. Today's biotech companies are benefiting long after patents expire and are profiting at the expense of all Americans. No employer, labor organization or health plan can continue to offer affordable coverage without competition in the biopharmaceutical industry. Without the ability to access less expensive, comparable, and interchangeable biopharmaceuticals, CalPERS ultimately will be forced to increase prescription drug co-pays or increase premiums, shifting the increasingly unaffordable costs onto the individuals who can least afford them.

Finally, I would like to address the issue of safety. Opponents of this legislation—primarily the biotech industry—are claiming that those who support the Access to Life-Saving Medicines Act are ignoring the safety threat of bringing biogenerics to the marketplace. I want to be clear—the safety and health of our members comes first in any decision we make about any policy. That is why we strongly support providing FDA with full discretion to make the ultimate decision about whether and when any prescription drug product, whether it be brand or generic, comes to market. The Access to Life-Saving Medicines Act does provide the FDA with that discretion.

CalPERS is proud and honored to add our support to the growing list of workers, seniors, patient groups, businesses, health plans, health care providers, pharmacy benefit managers and countless others who support the Access to Life-Saving Medicines Act to open the door to biogeneric competition. We stand ready to work with the Committee to pass legislation to give FDA the authority to approve safe and effective biogenerics as a means to providing consumers with affordable alternatives to high-cost biopharmaceuticals. Thank you for the opportunity to provide testimony for the hearing record.

STATEMENT OF COALITION FOR A COMPETITIVE PHARMACEUTICAL MARKET

Thank you Chairman Pallone, Congressman Deal, and members of the Subcommittee on Health. The Coalition for a Competitive Pharmaceutical Market (CCPM) appreciates the opportunity to submit this statement to the hearing record. We commend you for holding this important hearing on the need to establish a workable, safe and science-based regulatory pathway within the Food and Drug Administration (FDA) for the approval of biogeneric products.

BACKGROUND

CCPM is an organization of employers, health plans, pharmacy benefit managers, chain drug stores, generic drug manufacturers, and others committed to a competitive pharmaceutical market that expands access to affordable prescription medications. To achieve this outcome, we believe we must remove barriers to competition and choice that generic drugs bring to the market. We also need to develop new pathways to bring that same competition to the marketplace as it relates to biopharmaceuticals. Monopolies, such as what currently exist in this arena, are not only detrimental from a consumer and business perspective, they actually remove incentives for innovation. This helps explain our commitment to the establishment of a workable pathway for biogenerics.

As employers, including some of the Nation's largest manufacturers, it is imperative that our employees have access to safe and affordable prescription medications for two reasons. First, a healthy and productive workforce is critical to our ability to compete in a global economy. Second, the high cost of health care is limiting our ability to compete with other nations, and pharmaceuticals are the single fastest growing segment of overall health care costs. As health plans and pharmacy benefit managers, access to safe and affordable prescription medications is critical to our ability to slow the rate of growth in health insurance premiums for businesses and consumer out-of-pocket costs. As chain drug stores, we are on the front line as witnesses to the impact of high-cost prescription drugs on consumers. Finally, as generic drug manufacturers, we are committed to producing safe and affordable generic alternates to employers and consumers. Our membership is diverse, but we are united in our belief that a definitive regulatory pathway for the approval of biogenerics is critical to improving our Nation's health and controlling prescription drug costs.

VIEW ON PRESCRIPTION DRUG MARKETPLACE

CCPM strongly supports a vigorous and competitive prescription drug market, one in which innovation leads to new life-saving medicines. Currently competition is limited in the biopharmaceutical market because the FDA does not have the clear authority to approve biogeneric products. As a result, even when a patent has expired on a brand biopharmaceutical, the lack of a pathway thwarts competition, and keeps biopharmaceutical prices artificially high. CCPM urges Congress to find a bipartisan solution to create an appropriate regulatory route for FDA review of biogenerics. We believe the solution should grant the FDA the authority to use its discretion and scientific expertise to evaluate interchangeable and comparable biogeneric products while ensuring patient safety.

HATCH-WAXMAN LAW

One of the most important health care laws enacted over the past 30 years was the Drug Price Competition and Patent Term Restoration Act of 1984—commonly known as the Hatch-Waxman law. This landmark legislation broke important new ground in granting FDA the authority to approve generic versions of prescription products. Hatch-Waxman also gave FDA express authority to provide an abbreviated approval process for those products deemed equivalent to the prior approved product. It is estimated that this law saves patients and payers billions of dollars each year. We believe that bipartisan legislation introduced this year by Representatives Waxman and Emerson, H.R. 1038, the Access to Life-Saving Medicine Act, is an important next step in ensuring that biologic prescription drugs are more affordable and accessible. CCPM supports this important legislation, which will provide the clear authority that the FDA needs to approve biogenerics and bring much-needed competition to the biopharmaceutical market.

CONSUMERS AND PURCHASERS WILL BENEFIT WITH GREATER INNOVATION AND GREATER COMPETITION

Total spending on prescription drugs in 2006 is estimated at $213.7 billion and is expected to rise to $497.5 billion by 2016. [1]

The use of biopharmaceuticals is increasing at almost twice the rate of traditional medicines accounting for approximately $30 billion in U.S. sales and 12 percent of total pharmaceutical usage last year. [2]

The reason for the dramatic increase becomes clear when one examines the cost biopharmaceuticals compared to synthetic drugs. The average cost of a biopharmaceutical is $45 per patient per day, versus $1.66 per patient per day for a synthetic drug. These medicines can and do improve the lives of millions of patients—but without generic versions, the costs may keep needed treatments out of the hands of many consumers.

Providers of prescription drug coverage, both in the private sector as well as the Federal Government through programs such as Medicare and Medicaid, depend heavily on the role of generic products to help control costs. The lack of certainty in the prescription drug marketplace, particularly in the biopharmaceutical sector, poses great challenges to payers. Forecasting future health care expenditures remains difficult because there is no clear timeline for when or even if there will be lower cost alternatives for biopharmaceuticals. Many of the biopharmaceuticals on the market today are "off-patent" and more than $10 billion worth of biopharmaceuticals are expected to come off patent by 2010, [3]

GUIDING PRINCIPLES FOR BIPARTISAN LEGISLATION

When considering legislation to provide a clear regulatory pathway for the approval of biogenerics, CCPM encourages Congress to consider five key principles:

1. Protect and promote fair and open competition. CCPM members are leaders within their industries, and highly competitive. Several Coalition members are patent holders, and as such, respect and understand the development of innovation and need for patent protections. However, we strongly believe that once a patent expires or is successfully challenged, biogeneric competition should be able to enter the market.
2. Provide a definitive pathway for the approval of biogenerics. We believe there must be certainty in both timing and method of the biogeneric approval process. FDA needs the authority to approve both comparable and interchangeable biogeneric products. Congressional deference to the FDA's expert scientific judgment is appropriate. In addition, any action should permit prescribers and pharmacists to substitute one biologic for another when appropriate.
3. Encourage consistent and uniform terminology. Whether the terms are "comparable," "interchangeable," "therapeutic equivalent," or "generic"—we want an abbreviated process that results in a "biogeneric," meaning a lower cost alternative to biologic pharmaceuticals.
4. Increase resources for the Food and Drug Administration.In order to adequately assume these new responsibilities, the FDA will need adequate resources. We support additional resources for FDA to secure more staff to ensure the timely review of biogeneric applications and the safety of biogenerics for consumers.
5. Include the new legal authority for a biogeneric pathway in must-pass legislation this year.

We encourage Congress to move quickly to establish a regulatory pathway for the approval of biogenerics. We are confident this hearing will affirm the science for comparable and interchangeable products has arrived. Once the FDA has the discretionary authority to begin this process, it will drive innovation that will assist in the identification of similar and substitutable methods for these off-patent products. Each day that passes without biogenerics is another day of limited options. No payer, whether individual or employer, public or private, can afford unlimited monopoly pricing. CCPM is encouraged to hear reports that members are committed

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1 Poisal, J.A., et al, "Health Spending Projections Through 2016: Modest Changes Obscure Part D's Impact", Health Affairs 26, no. 2 (2007) Exhibit 6.

2 MedAdNews, November 2006 .

3 Engel & Novitt, LLP, "Potential Savings That Might Be Realized by the Medicare Program From Enactment of Legislation Such as The Access to Life-Savings Medicine Act (H.R. 6257/ S. 4016) That Establishes A New cBLA Pathway For Follow-On Biologics. Table 4a. , January 2, 2007 so the sooner these lower cost biogenerics can enter into the marketplace, the better. Additionally, when exploring avenues to introduce competition into the marketplace, CCPM urges Congress to clearly outline a reasonable process for early resolution of patent disputes to avoid any unintended loopholes and ensure certainty for the biogeneric marketplace.

to including a workable pathway in FDA Revitalization efforts, including the prescription drug reauthorization legislation (PDUFA) and strongly support you in this endeavor.

CCPM is pleased that the Energy and Commerce Health Subcommittee is considering issues like biogenerics that can make a positive impact on our health care system. We believe a bipartisan bill that empowers the FDA to use the best science to encourage innovation and biogeneric competition should be passed this year. The Waxman-Emerson-Pallone bill certainly meets this standard and, as such, CCPM has called for—and is urging—its passage. However, like the sponsors of this legislation, we well understand that there will be compromises to make before any bill is signed into law. What must not be compromised is safety as well as a workable, science-based pathway to provide competition and choice to consumers, employers, health plans and Federal, state, and local purchasers of pharmaceuticals. The very act of holding this hearing represents an important step to achieving this outcome and ending the unsustainable monopoly that currently exists. We commend you, Chairman Pallone, for taking this step and we look forward to working with you and all the other members of the Subcommittee and full Committee on this important issue.

COALITION FOR COMPETITIVE PHARMACEUTICAL MARKETPLACE (CCPM) MEMBERSHIP

April 2007

Aetna Inc, America's Health Insurance Plans, Apotex, Barr Laboratories, Ben Venue Laboratories, Blue Cross Blue Shield Association, Caremark, Caterpillar, Inc., DaimlerChrysler Corporation, Eastman Kodak Company, Express Scripts, Ford Motor Company, General Motors Corporation, Generic Pharmaceutical Association, Hospira, Humana, Kaiser Permanente, Medco, Mylan Labs, National Association of Chain Drug Stores, National Association of Health Underwriters, Pharmaceutical Care Management Association, Ranbaxy Pharmaceuticals, Teva Pharmaceuticals USA, Wallgreens Company , Watson Pharmaceuticals, Wellpoint

AARP STATEMENT FOR THE RECORD ON

ASSESSING THE IMPACT OF A SAFE AND EQUITABLE BIOSIMILAR POLICY IN THE UNITED STATES

SUBMITTED TO THE

HOUSE ENERGY AND COMMERCE HEALTH SUBCOMMITTEE

May 2, 2007

WASHINGTON, D. C.

For further information, contact:
Anna Schwamlein Howard/Kirsten Sloan
Federal Affairs Department
(202) 434-3770

On behalf of AARP's more than 38 million members, we thank you for holding this hearing and examining the issue of creating a pathway for generic biologics. AARP has endorsed the Access to Life-Saving Medicine Act (H.R. 1038) because we believe this legislation will create a much needed pathway for the approval of safe, comparable, and interchangeable versions of biologics. We call on Congress to pass the legislation this year.

Older Americans use prescription drugs more than any other segment of the U.S. population, and as a result, AARP is deeply committed to providing our members – and all Americans – access to safe, affordable prescription medications. Modern medicine increasingly relies on prescription medications. These prescription medications can come in many forms – such as traditional prescription drugs (small molecule compounds that are chemically manufactured), and the increasingly-used biological products (a more complex drug that is typically derived from a living source).

Generic traditional prescription drugs have helped improve the well-being of many individuals because they provide a safe, lower-cost alternative treatment. The benefit of affordable generic drugs extends beyond just economics: among patients with three-tier pharmacy benefit plans, researchers found that patients who began on generic prescriptions had a 62 percent greater chance of staying on their medicine compared to those who began on "nonpreferred" medicines.[1]

Though cost is a paramount concern, no prescription drug should be allowed on the market if it is not safe and effective for its intended purpose. This is why the FDA is tasked with ensuring the safety and efficacy of all prescription drugs on the market today, including biologics. While biologics are more complex than traditional prescription drugs, complexity alone has not prevented the FDA from approving brand name biologics, and it is not a valid reason to prevent research

[1] Shrank WH, Hoang T, et al., "The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions," *Archives of Internal Medicine,* Vol. 166, Feb. 13, 2006.

into the development of generic versions. Technology has progressed to the point where biologics are better understood and characterized – a statement we could not have made when the Hatch-Waxman Act was passed in 1984. As a result, it is now possible to create generic versions of these treatment therapies.

The Access to Life-Saving Medicines Act grants FDA the authority to create a pathway for the generic approval of biologics. The legislation simply mandates that FDA provide for a workable pathway of approval. And the legislation leaves the scientific determinations up to those who are best equipped to address them – the FDA. Common sense alone tells us that the agency that has the scientific knowledge to approve a brand-name biologic surely has the ability to provide a pathway for generic approval of the same biologic.

Moreover, the FDA has already approved a few generic biologics (or follow-on protein products). For example, last year, using authority granted to it under the Hatch-Waxman Act, the FDA approved Omnitrope, a generic version of the biologic drug somatropin, a human growth hormone. Unfortunately, there is still a need for Congress to pass legislation – such as the Access to Life-Saving Medicines Act – because most biologics are regulated under the Public Health Service Act for which there is no pathway for the approval of generic products.

While many of our members have benefited from biologics, still many others are not able to afford these treatment options. For example, one AARP volunteer, Bonnie, suffers from severe rheumatoid arthritis. Over the years, she has undergone a variety of treatment options, including a biologic drug Enbrel, which has helped her. Bonnie has encountered many people who suffer from her condition who are not able to afford the medication, which can cost $12,000 per year. One particular woman Bonnie encountered was so affected by the disease that her fingers were gnarled, she had difficulty walking, and she used all her energy just to get through a day. This woman recounted how she was trying to find a way to get access to Enbrel but could not due to the high cost of the drug.

Bonnie tells it best in her own words: "Having lived with this disease for 40 years, I know how incapacitating it can be and how the pain can be unbearable. I know what hope biologics can give to someone whose whole life is affected. To know that it cannot be obtained by other people with deadly diseases is brutal. How do you tell someone that they cannot have a treatment that may alter their life significantly?"

Use of biologic drugs is increasing every year[2] to treat diseases and conditions such as cancer, multiple sclerosis, anemia, and rheumatoid arthritis. Research and development into this vital field is growing – of the total pipeline, 27 percent of products are biologics.[3] These treatment therapies are, in many cases, truly cutting edge technology. For someone who has rheumatoid arthritis, a biologic treatment therapy can make the difference between having the ability to walk and having to live with debilitating, constant pain.

While biologics hold great promise for treating some of the most serious diseases, these treatment regimens can be very expensive. Some treatments can cost tens of thousands of dollars per month or hundreds of thousands of dollars per year. For example, Epogen, a drug used to treat anemia, can cost over $5,000 per year. In 2005, Medicare (which covers Epogen through its end-stage renal disease program) paid $2 billion for Epogen, more than for any other single drug.[4] Cerezyne, used to treat Gaucher disease, can cost as much as $200,000 per year – which is almost as much as the average price of a home in January 2007.[5] Similarly, a person diagnosed with colon cancer may be

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[2] Biotech Drugs Come of Age; Policymakers Take Note, Health Affairs, Sept./Oct. 2006 (reporting that in 2005 revenues for biological drugs totaled $50.7 billion, an increase of 15.8 percent over 2004).
[3] IMS Health, press release, March 20, 2007.
[4] "Dialysis Profits May put Patients at Risk," Associated Press, April 19, 2007.
[5] National Association of Realtors data, available at http://www.realtor.org/research/index.html (reporting the existing home median price was $210,000 in January 2007).

prescribed Avastin, which can cost $100,000 per year, more than the average cost of a four-year college education.[6]

Some individuals are fortunate enough to have insurance coverage and/or the means to be able to afford these medications. However many are not so lucky. The astronomical cost of biologics not only impacts consumers, but also health care payers such as employers, private health care plans, and public programs like Medicare and Medicaid. In fact, growth in spending on biologic drugs continues to outpace even that of traditional brand name prescription drugs. Total U.S. prescription drug sales grew 8.3 percent to $274.9 billion in 2006. Biotech products again remained a major growth engine in 2006, with sales increasing 20 percent to $40.3 billion.[7]

The U.S. health care system – including federal and state governments, employers, insurers, and consumers – cannot continue to sustain these astronomical prices. It is critical that we begin to take steps to lower the cost of these biologics. One way to control these costs is to provide a pathway for the approval of generic versions of these products.

History tells us that lower priced drugs can be brought to market safely and effectively. As a result of the Hatch-Waxman Act, today, generic prescription drugs save consumers and health care payers billions of dollars each year.[8] Almost 57 percent of all prescriptions, and nearly two-thirds of all new prescriptions (63.8 percent), were filled with generics in 2006.[9] Also, among

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[6] College Board, Trends in College Pricing 2006, available at http://www.collegeboard.com/prod_downloads/press/cost06/trends_college_pricing_06.pdf (reporting that average total tuition and fees at a four-year private college or university for the 2006-2007 academic year was $22,218).
[7] IMS Health Report, March 2007. http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_80415465,00.html.
[8] CBO, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.
[9] "Drug Topics," April 2, 2007.

Medicare Part D prescription drug plans, generic utilization was over 59 percent in the third quarter of 2006, according to CMS.[10]

Those who oppose creating a pathway for the FDA to approve generic biologic drugs have claimed that lowering prices would hinder research and development efforts. This argument, similar to opposition claims at the time Hatch-Waxman was enacted, again rings hollow. In 1984, critics claimed that as a result of generic prescription drugs, consumers would suffer because companies would no longer invest resources to find new cures. History has proven these critics wrong. More consumers than ever have access to more affordable generic drugs. And the pharmaceutical industry – now the fifth most profitable industry in the country[11] – has been hugely profitable.

With scientific advances, prescription drugs have become an increasingly important component of health care, and biologic drugs will become an even larger component of drug spending. When brand name prescription drugs go off patent, a generic manufacturer can begin marketing its lower cost alternative after being approved by the FDA. The time is now to create such a pathway for biologics. Today, manufacturers continue to reap the rewards of their patent long after its expiration. As a result, consumers continue to pay high prices for biologics, and it costs the health care system billions of dollars more.

The Hatch-Waxman Act created an abbreviated pathway for the approval of generic drug applications, and consumer and health care payers benefited. Now Congress has the opportunity to pass the Access to Life-Saving Medicines Act, which gives the FDA the authority to approve generic versions of biologics. Once this legislation has been enacted, consumers and health care payers can begin to see savings on these life saving medications.

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[10] CMS press release, Feb. 8, 2007.
[11] Fortune 500 2006, "Most Profitable Industries: Return on Revenue," April 17, 2006.

Conclusion

The Hatch-Waxman Act created a pathway for FDA to approve generic prescription drugs. Twenty-three years later, the time has come for generic approval of biologics. The Access to Life-Saving Medicines Act provides FDA the authority to produce a safe, comparable or interchangeable version of a biologic, and scientific advancements now ensure FDA has the ability to approve generics safely.

Our members, and all Americans, need Congress to enact this bi-partisan legislation this year. We are pleased to see this Committee, and Members from both Houses of Congress and both sides of the aisle, moving forward on this issue.

815 SIXTEENTH STREET, N.W.
WASHINGTON, D.C. 20006

LEGISLATIVE ALERT!

(202) 637-5090

JOHN J. SWEENEY
PRESIDENT

RICHARD L. TRUMKA
SECRETARY-TREASURER

LINDA CHAVEZ-THOMPSON
EXECUTIVE VICE-PRESIDENT

May 1, 2007

The Honorable Henry A. Waxman
U.S. House of Representatives
2204 Rayburn House Office Building
Washington, D.C. 20515

Dear Representative Waxman:

I am writing to urge timely consideration of the Access to Life-Saving Medicine Act (H.R. 1038), which will provide statutory authority for the Food and Drug Administration (FDA) to approve generic versions of biopharmaceuticals (also known as biotech drugs). This legislation, which will increase competition in the biopharmaceuticals market, represents a significant opportunity to rein in escalating health care costs while increasing access to life-saving drugs.

Biotech drugs, which are produced from living cell cultures rather than synthesized chemically, hold enormous promise for treating illness and disease, but they can be prohibitively expensive. For example, Avastin is used to treat colon cancer and, with recent approval, breast cancer, but it costs $100,000 per year. Cerezyme, a drug used to treat a genetic condition, is priced at an average of $170,000 per year. In the absence of FDA authority to approve generic versions, these and other biotech drugs will essentially retain their patents permanently, pricing the drugs beyond reach for many patients and exploding costs for health plans and taxpayer-financed programs that provide coverage for them. Currently $12 billion of the biotech drugs sold each year no longer have patent protection, but under current law they are not subject to generic competition.

Generic drugs currently available have produced substantial savings for patients and payers – over $10 billion per year. Given the significant cost of most biotech drugs, we can expect even more savings will result from generic biotech drugs without compromising patient care. These savings – for Medicare, Medicaid, private health insurance and patients – will help make coverage more affordable for all Americans.

This year's review of the Prescription Drug User Fee Amendments reauthorization and other FDA legislation provides the optimal opportunity for Congress to enact a workable pathway for FDA approval of generic biotech drugs. The AFL-CIO urges Congress to take up the Access to Life-Saving Medicine Act during this Congress's review of the FDA.

Sincerely,

William Samuel, Director
DEPARTMENT OF LEGISLATION

Testimony of Scott McKibbin
Special Advocate for Prescription Drugs
State of Illinois

Testimony Submitted to the House Energy and Commerce Subcommittee on Health

Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States

May 2, 2007

Thank you for the opportunity to submit testimony for the record on behalf of Illinois Governor Rod R. Blagojevich in support of establishing a pathway for generic biopharmaceuticals. I want to applaud Chairman Pallone for his vision in recognizing that the escalating costs of biopharmaceuticals to states and consumers is creating an economic burden on Illinoisans, and state budgets nationwide. These costs will continue to make it more difficult to balance cost control and access for patients to affordable life-saving biopharmaceuticals both in Illinois and the nation as a whole.

By way of background, I have more than 19 years of experience consulting to large public entities, employers, and foundations on a variety of health care issues.

In my present role as the Special Advocate for Prescription Drugs, I have functional accountability for overseeing the $2.8 billion dollar annual prescription drug spend for the State of Illinois. My duties include working across agencies and programs to ensure the residents and taxpayers of Illinois are well served. I am also a two-time kidney cancer survivor, and can speak from personal experience on both the value and costs of therapies that treat such dreaded diseases as cancer.

The State of Illinois has a long history of recognizing the need to provide prescription drug assistance to our residents. Illinois was the first state to successfully obtain and implement an 1115 wavier for a SeniorCare Pharmaceutical Program, which expanded prescription drug coverage to seniors and disabled residents, based on income limits. Predating our SeniorCare Program, Illinois maintained a State Pharmaceuticals Assistance Plan (SPAP) for drugs to treat ten (now eleven)-diseases.

Under the leadership of Governor Rod R. Blagojevich, Illinois offers **the most** comprehensive Part D wraparound program (Illinois Cares Rx) in the country. And, as of last summer, Illinois offers to EVERY child in Illinois access to health insurance coverage (including prescription drugs) under our AllKids Program.

I want to make it clear that I have a dual role as Special Advocate. The State of Illinois, as does every state, has the responsibility to ensure that the prescription pharmaceuticals available to consumers are safe and effective. So I would like to dispense with the issue of safety as a given for the discussion of any generic legislation.

From our perspective, creating a process that enables the Food and Drug Administration (FDA) to determine the safety and interchangeability of biopharmaceuticals must be a given. The traditional generic pharmaceutical industry, which was created with the landmark Hatch/Waxman Act of 1984, established a process that tasked FDA with determining how to ensure generic versions of traditional pharmaceuticals could be scientifically determined to be safe, effective and interchangeable with their brand name counterparts.

While some in this debate are seeking to obscure the real issues with inflammatory rhetoric about the potential lack of safety of generic biopharmaceuticals, it is my position that this legislation authorizes FDA to take those scientifically sound steps that are appropriate to ensure the safety of generic biopharmaceuticals.

This is an appropriate role of the FDA, as the agency has the expertise and experience to handle this task. After all, it is the FDA that is charged with overseeing the process for approval of these biopharmaceuticals in the first instance. As a result, I believe that the science is available today to establish a process that will ensure the timely approval of generic versions of biopharmaceuticals. Authorizing FDA to do what it does best, determine which scientific goal posts are necessary to approve a safe and effective generic, should be beyond the debate of this legislation. I am confident that once the FDA process has been established that the value of generic competition for consumers will become obvious.

The Reality of Biopharmaceutical Costs

I want to focus the bulk of my testimony on the reality of biopharmaceutical costs, and the value of generic competition in this arena. Illinois is a partner with the Federal Government in providing and paying for prescription drugs. We are also responsible for providing and nurturing a sound economy in our state, one that does not allow healthcare costs to bankrupt our state, or negatively impact employers or the overall business climate of our state. To this end, Governor Blagojevich has introduced a comprehensive program to expand or offer coverage to the 1.4 million uninsured between the ages of 19 and 64 and to offer relief to many of our residents who struggle every day to pay for the healthcare cost covered under existing insurance plans.

There should be little debate about the cost of providing prescription medicines. And while there may be some debate about the actual rate of increase of expenditures for biopharmaceuticals, the fact remains that the impact on Illinois of these costly drugs is growing dramatically and will reach a crisis within the foreseeable future.

As I said, there is some debate about whether the annual increase in the cost of biopharmaceuticals is 15%, 17% or 20%. But the difference is, in fact, not material. If, as I believe and my data shows, that expenditures for these products are rising at an average of 15% annually, then within five years what Illinois spends on these drugs today will double. That will have a dramatically negative effect. We will not be able to afford these medicines.

Analysis of Illinois Biopharmaceutical Expenditures
Many states probably don't even realize the depth of what they are spending now on biopharmaceuticals. According to IMS, biopharmaceutical sales in 2006 grew to $40.3 billion. While spending has escalated, a debate over the potential for generic biopharmaceuticals has spanned four FDA commissioners, all with varied levels of prioritization on how to establish a biopharmaceutical generic approval process. States need more than continued discussion on this issue. We need action. Chairman Waxman's bill is a great first step in actually getting us on the road to creating a framework to permit generic competition and the savings it will create.

To understand the breadth of the impact of spending on biopharmaceuticals for Illinois, we examined leading biopharmaceutical products and what the state of Illinois spent on these products. The results were staggering.

For our 227,500-member employee/retiree group, the State of Illinois spent $33.2 million dollars for a select list of approximately 100 biopharmaceuticals during the fiscal year ending June 30, 2006.

This amount (without trend) represented over 12% of the entire plan cost and is growing at an astronomical rate on both the price and utilization side of the ledger. The ingredient cost increase was 49.9% and the plan cost increase per member was 50.3%.

The number of prescriptions for this select list of biopharmaceuticals also rose significantly, a nearly 29% increase.

Programs administered under the State Medicaid Agency will have seen similar cost and utilization increases, but on a much larger scale. For the most recent year in which data is available, the cost of 61 biopharmaceuticals was $100,662,000 paid for under the pharmacy benefit and estimated $75 million paid for under the medical and Part D wraparound programs. The grand total exceeds $200 million per year, without trend.

In order to better understand the impact for individual patients, we looked at cost for selected biopharmaceuticals. For example, patients in our State Employee Group requiring Traceer™, used to treat a condition of high blood pressure in the lungs, cost $28,300 per patient, per year; patients requiring Actimmune®, used to treat both children and adults with chronic granulomatous disease (CGD) and osteopetrosis, cost $38,566 per patient, per year. And finally, patients prescribed Genotropin®, for long-term treatment of growth failure in different conditions, cost $17,588 per patient, per year.

Potential for Cost Savings
Now, much has been said about the potential cost savings of generic competition. Opponents to creating a pathway for generic competition argue that the cost savings may only be 10 or 20 percent. Let's look at the worst case savings – 10%. If Illinois were able to reduce the 15% annual increase in spending in biopharmaceuticals by even 10%,

then we not only extend our ability to pay for these drugs, but we also extend our ability to continue, under state programs, to provide increased access to them.

And in fact, a 10% or 15% initial savings will equate to real dollars for Illinois. Based on our analysis, $25 to $37 million per year (without trend).

Any savings on these expensive drugs will be welcomed. Even a 10% discount on a $38,000 treatment biopharmaceutical is substantial to our state budget, especially when this savings is compounded over several years. In considering the potential for savings from generic competition, I implore Congress to look not only at their cost today, but also at the impact of savings as a result of the growing usage that has resulted as indications are broadened and as more consumers, who have exhausted other therapeutic options for critical conditions, are prescribed biopharmaceuticals.

The other issue to consider about savings is this – it appears an obvious one from my perspective, but seems lost in the debate: In the past year, biopharmaceutical expenditures have increased at double-digit rates. If we do nothing for the rest of 2007, we will end the year with even higher expenditures associated with biopharmaceuticals. Every day that we delay in creating a pathway for generic competition is a day of potential savings lost to states, to taxpayers, to consumers. We cannot afford to wait any longer to begin to save, even if, as opponents predict, that savings will initially only be modest.

Summary: The Time is Now
We must begin on the pathway to creating an approval process for generic biopharmaceuticals today. Every day we delay is a day of potential savings lost, and a day of escalating expenses. And although this may sound dramatic, it is a day closer to Illinois and other states drowning in the red ink of drugs we cannot afford to give to patients that need and deserve them. It is also another day lost for employers, who are seeing an increasing percentage of their healthcare expenses grow as a result of increased usage of biopharmaceuticals.

I urge Congress to approve legislation that will authorize the FDA to apply sound scientific regulatory criteria that will give Illinois, all other states, and every consumer and taxpayer lower cost biopharmaceutical products, and increased access that results from the cost savings.

May 21, 2007

Geoffrey Allan, Ph.D.
President, CEO, Chairman of the Board
Insmed Incorporated
8720 Stony Point Parkway, Suite 200
Richmond, VA 23235

Dear Dr. Allan:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 2, 2007, at the hearing entitled "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from a certain Member of the Committee. In preparing your answer to these questions, please address your response to the Member who has submitted the questions and include the text of the Member's question along with your response.

To facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Friday, June 1, 2007**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Melissa Sidman, Legislative Clerk/Public Health. An electronic version of your response should also be sent by e-mail to Ms. Melissa Sidman at **melissa.sidman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Anna G. Eshoo, Member
Subcommittee on Health

INSMED
INCORPORATED

June 7, 2007

John D. Dingell, Michigan
Chairman
U.S. House of Representatives
Committee on Energy and Commerce
Washington, D.C. 20515-6115

Dear Chairman Dingell:

I am writing in response to your letter dated May 21, 2007. The following are my comments on the questions received.

First Question: I have read your testimony and understand your concerns about the costs of drugs and biologics, and rising medical costs, in general. I certainly share many of the same concerns.

- If biologics are so prohibitively expensive, why do you pay for them?
- Why do you include them in your formulary?

I am a CEO of a Biotechnology company and do not make formulary decisions and therefore not the right person to address this question.

However, I would like to make the following comments. I do not believe that biologics are prohibitively expensive. I believe in many cases these drugs play a valuable role in combating disease and in some cases prolong or save lives. I believe the price is justified to allow the innovator company to recoup investment and ensure continued innovation. However, there comes a time when that investment has been recouped and there needs to be an opportunity for competition to be brought into the market to stimulate lower prices. The patent protection and data exclusivity periods afforded these drug provide adequate time for the investment to be recouped.

Second Question: As you know, under *Hatch-Waxman*, major pharmaceutical manufacturers are provided a five-year period of data exclusivity for new drugs, and are not limited in their legal rights to prevent infringement of their patents in the manner contemplated under the legislation you advocate. Biotech discoveries are much riskier and more expensive to develop than traditional pharmaceuticals, but often provide the only effective treatment available.

- Why should the biotechnology industry receive less favorable incentives for innovation and less favorable procedural rights in litigation than traditional drug manufacturers?
- Is it right to give greater incentives for the next Rogaine or Viagra than the next EPO or Avastin? How do you justify this?

9720 Stony Point Parkway • Suite 200 • Richmond Virginia 23235 • Phone: 804.565.3000 • Fax: 804.565.3500

INSMED
INCORPORATED

With regard to this question I would like to make some remarks regarding the statements within the question.

What is the evidence that Biotech discoveries are more riskier and more expensive to develop than traditional pharmaceuticals? Lacking hard evidence for this statement makes the question difficult to answer.

I have been in the industry developing drugs for nearly 30 years both of a traditional and biologic nature, I do not believe this statement is correct. The same level of investment in terms of research dollars is required to develop either class of these drugs and the risks and uncertainties are no different. Therefore, on the surface I would argue that both classes of drugs should be afforded the same protection and provided the same incentives.

I also think it is offensive to the traditional pharmaceutical industry to suggest that the sum total of their innovation is the development of Rogaine and Viagra. Over a long period of time the Pharma industry has produced drugs of great value in all therapeutic classes and no less valuable than Avastin.

Drugs for the treatment of heart disease, high blood pressure, diabetes, infectious diseases, most if not all CNS disorders all came from the Pharma industry. They are small molecules subject to generic competition. Why should Avastin or Epogen be considered more important and given special privilege.

I am happy to discuss these topics in more detail. Please contact me at gallan@insmed.com or (804) 565-3010.

Warmest regards,

Geoffrey Allan, PhD
President & CEO
Insmed Incorporated

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Anna G. Eshoo, Member
Subcommittee on Health

May 21, 2007

Mr. Bruce Downey
Chairman and CEO
Barr Pharmaceuticals, Inc.
400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Mr. Downey:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 2, 2007, at the hearing entitled "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from a certain Member of the Committee. In preparing your answers to these questions, please address your response to the Member who has submitted the questions and include the text of the Member's question along with your response.

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Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Anna G. Eshoo, Member
Subcommittee on Health

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 1, 2007

The Honorable John D. Dingell
Chairman, Committee on Energy and Commerce
2328 Rayburn House
Office Building
Washington, DC 20515

Dear Chairman Dingell:

On behalf of Barr Pharmaceuticals, as well as the millions of American consumers we serve each year, I want to once again express my appreciation for being allowed to testify at the May 2, 2007 hearing before Subcommittee on Health entitled "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." Given the considerable importance of this issue to all Americans, I appreciate the opportunity to provide the following comments in response to your May 21, 2007 letter, which contained two questions posed by Representative Anna G. Eshoo.

QUESTION #1

I have read your testimony and understand your concerns about the costs of drugs and biologics, and rising medical costs, in general. I certainly share many of the same concerns.

- If biologics are so prohibitively expensive, why do you pay for them?
- Why do you include them in your formulary?

RESPONSE:

This question appears to be directed at witnesses such as Dr. Ed Weisbart, who testified on behalf of Express Scripts. Nevertheless, Barr shares your concern about the high cost of pharmaceuticals in general, and the high cost of biological medicines in particular. According to IMS Health, in 2006 prescription drug sales were up 8.3% to $274.9 billion. (Source: Business Wire 3/9/07).[1] Sales of biological drug products increased 20% overall in 2006 to $40.3 billion. (*Id.*). Sales of many frequently-prescribed biological medicines grew at an even higher rate. For example, Amgen's Aranesp® grew 42% to reach $3.9 billion; Avastin® rose 79% to $1.7 billion; Herceptin® increased 66% to $1.2 billion; and Amgen's Neulasta® climbed 28% to $2.9 billion. (*Id.*). Neulasta®, used to correct chemotherapy-induced white blood cell deficiency, costs an average $3,500 per chemotherapy cycle.

[1] Available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_80415465,00.html (last accessed 5/22/07).

Given these facts, everyone should agree that obtaining a legislative pathway that will give consumers and taxpayers prompt access to generic medicines is of critical importance. Such legislation will allow companies, like Barr, to provide consumers with safe and affordable versions of many of the life-saving biological medicines used in the treatment of diabetes, cancer, rheumatoid arthritis, HIV/AIDS and other diseases.

QUESTION #2

As you know, under *Hatch-Waxman*, major pharmaceutical manufacturers are provided a five-year period of data exclusivity for new drugs, and are not limited in their legal rights to prevent infringement of their patents in the manner contemplated under the legislation you advocate. Biotech discoveries are much riskier and more expensive to develop than traditional pharmaceuticals, but often provide the only effective treatment available.

- Why should the biotechnology industry receive less favorable incentives for innovation and less favorable procedural rights in litigation than traditional drug manufacturers?
- Is it right to give greater incentives for the next Rogaine or Viagra than the next EPO or Avastin? How do you justify this?

RESPONSE:

Effective generic biologics legislation will balance access to affordable generic medicines with encouraging continued innovation by brand companies. At present, however, the system only provides incentives for innovation. Indeed, the biotech industry has never faced generic competition even though it enjoys many of the incentives for innovation enacted in 1984 as part of Hatch-Waxman. Specifically, in addition to being granted twenty years of patent exclusivity from the date of invention for any patentable aspect of their branded biological products, Hatch-Waxman provides biotech companies with numerous patent-related extensions that can be used to lengthen their monopoly period:

- Hatch-Waxman permits brand biotech drug manufacturers to obtain upwards of 5 a year extension on their patent monopoly for time lost while the product was undergoing testing or awaiting government approval. (35 U.S.C. § 156).

- Hatch-Waxman also gives biotech manufacturers one day of exclusivity for every day over three years it takes to review a patent when the delay is caused by the PTO. (35 U.S.C. § 154(b)(1)(B)).

Current law also provides that biotech companies are eligible for certain regulatory exclusivity periods, as well as various tax credits, to spur innovation:

- Orphan Drug exclusivity permits drug manufacturers 7 years of market exclusivity for drugs intended to treat rare diseases. (21 U.S.C. § 360cc).

- Orphan Drug Tax Credits allow manufactures to claim a tax credit equal to 50% of the cost of human clinical trials for drugs intended to treat rare diseases. (26 U.S.C. § 45(c)).

- General Business R&D Tax Credits allow drug manufacturers to claim 20% of their qualified spending in the U.S. above a base amount. (26 U.S.C. § 41).

- Puerto Rico Activity Tax Credits allow U.S. corporations to exempt 40% of their income from business operations in Puerto Rico, the Virgin Islands, or other U.S. Territories. (26 U.S.C. § 936).

- Foreign Tax Credits permit U.S. corporations paying taxes to foreign governments to claim a limited tax credit for those payments. (26 U.S.C. § 901).

With these numerous special protections and incentives already available to the biotech industry, a credible argument certainly can be made that Congress need not give these companies additional ways to prolong their monopolies and deny the public prompt access to affordable biological medications. Indeed, take EPO, which is mentioned in Representative Eshoo's question. FDA approved Epogen/Procrit in 1989. Yet, *eighteen years* later, there is no less-expensive generic version of this product on the market and, if the biotech industry has its way, there will be no affordable version for years and years to come. The public, of course, very much needs an affordable comparable version of this drug – a drug for which Medicare spent at least $1.75 *billion* in just fiscal year 2005. (Source: CQ Weekly, 10/2/06).

Furthermore, any discussion of additional incentives quickly finds the brand industry demanding an entirely unjustified amount of time for data exclusivity. For instance, a March 2007 BIO "specification" for generic biologics legislation includes a 12-year filing moratorium for submitting generic applications and a 14-year marketing exclusivity period for innovator companies. Unfortunately, some members of both the U.S. House of Representatives and U.S. Senate apparently have endorsed this unwarranted barrier to generic market entry. H.R. 1956, introduced by Representative Inslee, contains BIO's proposed 12-year filing moratorium and 14-year marketing exclusivity period. So, too, does the S. 1505, introduced on May 24 by Senator Gregg. Such provisions are, of course, just two of the many provisions found in these bills that would significantly and unnecessarily delay the submission and/or approval of generic applications. Regrettably, those bills, like BIO's March "specification," also include provisions that would needlessly limit the saving that consumers and taxpayers would enjoy once generic products do enter the market. Examples of such provisions are: (1) the prohibition against an interchangeability determination absent additional action by Congress; (2) the requirement of unique nonproprietary names for generic biologics; and (3) the revisions to the FFDCA's labeling provisions.

Barr Laboratories, Inc.

Despite the incentives that already exist for brand companies to invest in new biological products, in order to obtain a workable pathway for the approval of generic versions of biological products, Barr would support a reasonable marketing exclusivity period for products containing new active ingredients. Barr cannot, however, support filing moratoriums, *i.e.*, provisions that prevent generic companies from submitting applications. H.R. 1956 contains two types of filing moratoriums: one that prevents a generic company from submitting an application for 12 years from the date of brand approval, and one that prevents the submission of an application until FDA completes a formal guidance process – a process that would take years. There simply is no legitimate justification for such provisions, which do nothing but delay generic market entry even on off-patent products that FDA approved more than a decade ago. Consumers and taxpayers need and deserve better.

With respect to procedural litigation rights, nothing in any currently pending generic biologics legislation negatively impacts a brand company's procedural litigation rights. It is true that the patent process found in H.R. 1038, for example, is different in some respects to the system found in Hatch-Waxman. This does not mean, however, that it negatively or unfairly impacts anyone's procedural litigation rights. Rather, the bill takes advantage of our 20-plus years of experience with the Hatch-Waxman system and improves upon it in ways that will allow patients quicker access to safe and affordable medicines. For example, brand companies have long used (and abused) Hatch-Waxman's 30-month mandatory stay of FDA approval to delay generic market entry. Congress stepped in to fix some of those abuses in 2003 as part of the MMA. Other abuses continue, however. H.R. 1038 employs a variety of statutory provisions to prevent these abuses when it comes to generic biologics.

To the extent that the brand industry wishes for strategic reasons to characterize these provisions as "limits" on their procedural rights, those provisions do not limit rights any more than Hatch-Waxman "limits" a generic company's procedural litigation rights. For example, Hatch-Waxman gives brand companies the right to select the judicial district in which suit will be brought by prohibiting a generic company from bringing a declaratory judgment action until the brand company has an opportunity to file suit in the district of its choice. *See* 21 U.S.C. § 355(j)(5)(B)(iii). We are not aware of competitors in other industries facing similar restrictions on their ability to bring declaratory judgment actions.

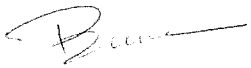
Finally, Representative Eschoo's question asserts that "[b]iotech discoveries are much riskier and more expensive to develop than traditional pharmaceuticals . . . ." Barr is unaware of any data supporting the idea that biologics are riskier to develop than traditional pharmaceutical products. Also, cost is relative. While some biologics may be costlier to manufacture, their development programs are not always as large as traditional pharmaceuticals. Take drugs used to treat rheumatoid arthritis as an example. Although it may cost more to produce them, as we understand it, they were approved with smaller studies (hundreds of patients) compared to traditional drugs, which often require thousands of patients for approval. And while there may be more biologicals approved to treat rare diseases, as noted above, the law currently affords orphan status and the seven years of marketing exclusivity that comes with that status.

Barr Laboratories, Inc.

In the end, Chairman Dingell, Barr supports a balance between access and innovation. Bills such as H.R. 1956, however, do not contain the needed balance. Rather, they are skewed so far in favor of the biotech industry that consumers and taxpayers would not see the introduction of safe and affordable generic versions of any biologic medicine for many years. Barr, therefore, encourages all members of Congress to consider the more balanced and carefully-crafted pathway proposed by H.R. 1038. Proposals such as that one will ensure the public has prompt access to safe and affordable drugs.

Should you or another other member of your Committee require any additional information, please do not hesitate ask. Barr looks forward to continuing to work with you and others in Congress on this important issue.

Sincerely,



Bruce L. Downey
Chairman and CEO
Barr Pharmaceuticals, Inc.

May 21, 2007

Ed Weisbart, M.D.
Chief Medical Officer, Medical Affairs
Express Scripts, Inc.
13900 Riverport Drive
Maryland Heights, MO 63042

Dear Dr. Weisbart:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 2, 2007, at the hearing entitled "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from a certain Member of the Committee. In preparing your answers to these questions, please address your response to the Member who has submitted the questions and include the text of the Member's question along with your response.

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Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Anna G. Eshoo, Member
Subcommittee on Health

Ed Weisbart, MD, CPE, FAAFP
Chief Medical Officer
One Express Way, Mailstop HQ2N02
St. Louis, MO 63121
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www.express-scripts.com

May 31, 2007

The Honorable John Dingell
Chairman, House Committee on Energy and Commerce
316 Ford House Office Building
Washington, DC 20515-6115

Attention: Melissa Sidman, Legislative Clerk/Public Health

Dear Chairman Dingell;

I am writing to respond to Representative Anna Eshoo's follow up questions following my testimony at the May 2 hearing entitled, " Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." Thank you for the opportunity to elaborate on Ms. Eshoo's questions. Specifically, Ms. Eshoo asked:

1. I have read your testimony and understand your concerns about the costs of drugs and biologics, and rising medical costs, in general. I certainly share many of the same concerns.
   - If biologics are so prohibitively expensive, why do you pay for them?
   - Why do you include them in your formulary?

2. As you know, under *Hatch-Waxman*, major pharmaceutical manufacturers are provided a five-year period of data exclusivity for new drugs, and are not limited in their legal rights to prevent infringement of their patents in the manner contemplated under the legislation you advocate. Biotech discoveries are much riskier and more expensive to develop than traditional pharmaceuticals, but often provide the only effective treatment available.
   - Why should the biotechnology industry receive less favorable incentives for innovation and less favorable procedural rights in litigation than traditional drug manufacturers?

- Is it right to give greater incentives for the next Rogaine or Viagra than the next EPO or Avastin? How do you justify this?

Frankly, there were others on my panel who would be more appropriate to address the second set of questions, however I will share our company's position. Express Scripts supports giving biotech companies incentives to develop important biotech drugs. Before Hatch-Waxman was enacted, an extensive case was made to Congress why patent extensions were necessary. Today, biotech companies are eligible for 20-year patents, 5 years of patent extensions (up to a maximum of 14 years), and 7 years of market exclusivity provided under the Federal Food Drug and Cosmetic Act.

In stark contrast, current law does not contain a mechanism by which the public can receive prompt access to affordable generic biotech medications. Express Scripts recognizes that legislation is often a matter of compromise, but it is critical that any such compromise not unduly deprive patients and payers the opportunity to purchase less expensive biotech drugs.

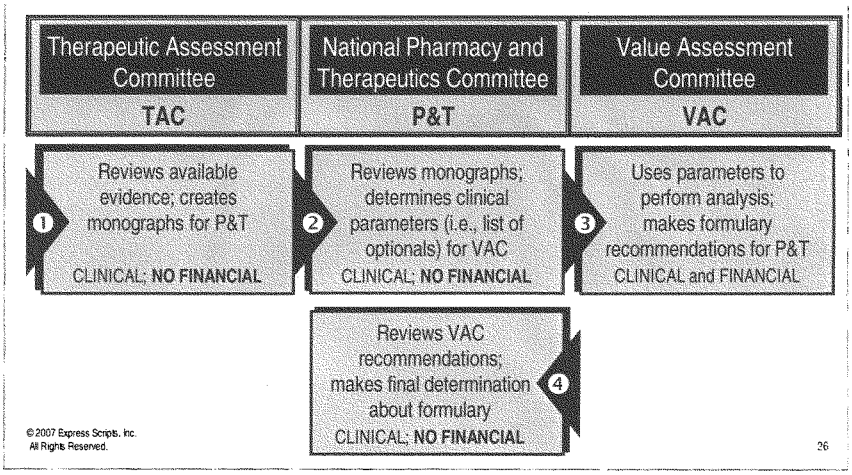
With respect to the first set of questions regarding the cost of biologics, the simple answer of why we cover them on our formularies, regardless of their costs, is that our formulary design is based upon clinical considerations. We can't— and wouldn't— exclude a biotech drug solely because of its cost.

I want to take this opportunity to engage in a thoughtful dialogue about formulary development as it applies to biologic agents. Our approach to formulary development is actually identical for traditional chemical pharmaceuticals and biologic agents.

Express Scripts acts on behalf of health-benefit plan sponsors and individual members of health plans to provide affordable access to clinically sound, high-quality pharmaceutical products. Drug formularies are one method of achieving this result. One of the key principles that guides all our actions in this area is that the *clinical appropriateness* of the drug, not cost, is our foremost consideration.

Express Scripts has many years of formulary-development expertise and an extensive clinical pharmacy department. Our formularies include virtually all generic medications and apply a rigorous process for identifying which brands are added in addition to those generic medications. Express Scripts develops formularies through a four-step process involving the work of the following committees:

1. Therapeutic Assessment Committee
2. Value Assessment Committee
3. National Pharmacy & Therapeutics (P&T) Committee



1. **Therapeutic Assessment Committee reviews literature and prepares initial recommendation for formulary positioning.** Composed of Express Scripts' clinical pharmacists and medical director, the Therapeutic Assessment Committee (TAC) focuses on primary drug review. This committee evaluates a drug after its approval by Food and Drug Administration (FDA). Pharmacists conduct a search of medical literature, review published data from clinical trials and the FDA-approved package insert. The TAC typically contacts the pharmaceutical manufacturer in order to obtain and evaluate additional safety and efficacy information that led to the product's FDA approval. The pharmacists may also contact physician specialists to obtain additional information and review medical practice guidelines relevant to the drug's approved indication. A thorough clinical review is conducted, including medication pharmacology, safety, efficacy, and dosage.

   The clinical information on the drug under review is then compared to clinical information on pharmacologic and non-pharmacologic therapy alternatives. After clinical evaluation, the TAC forwards to the Express Scripts National P&T Committee its recommended clinical designation (e.g., whether the drug should be included on or excluded from the Express Scripts National Formularies, whether it is optional for formulary inclusion, or whether it should be given a conditional include designation to meet the specific therapeutic needs of an identifiable subset of patients with a given condition).

- Drugs with a designation of Include are recommended for placement on all formularies. Drugs may be given an Include designation for one or more of the following clinical reasons: unique indication for use, efficacy superior to that of existing therapy alternatives, a safety profile superior to that of existing therapy alternatives, unique pharmacology, and/or a unique place in therapy.
- Drugs with an Exclude designation are not recommended for formulary inclusion. Drugs are given an Exclude designation for one or more of the following clinical reasons: efficacy inferior to that of existing therapy alternatives, a safety profile inferior to that of existing therapy alternatives, and/or insufficient data to evaluate the drug.
- Drugs designated as Optional are forwarded to the Value Assessment Committee for formulary consideration Drugs are given an Optional designation based on the assessment that they are clinically equivalent to currently available formulary alternatives and do not demonstrate a clinical reason for an "exclude" designation.
- Drugs in the Conditional Include category are recommended for inclusion on all ESI National Formularies after meeting a conditional qualification. Drugs in this category have a unique indication or place in therapy in an *identifiable* subgroup of patients within a broader set of less unique medical indications where more clinical choices are available. The ranking of conditional include is based on a case-by-case assessment which determines the need for a formulary exclusion override (*e.g.* an individual patient meets the criteria for access to the drug).

2. Express Scripts' National Pharmacy & Therapeutics Committee reviews TAC's recommendations and issues formulary construction parameters. The formulary recommendations from TAC are presented to the Express Scripts National Pharmacy & Therapeutics (P&T) Committee. The P&T Committee approves or disapproves the recommended clinical designations of TAC (*e.g.*, whether the drug should be included on or excluded from the formulary, whether it is optional for inclusion, or whether it meets the criteria for a conditional include designation). **In making its decision, the P&T Committee does not use price information in making a decision about the inclusion or exclusion of a drug from the formulary.**

If the P&T Committee does not approve TAC's recommended clinical designation for a drug, the designation is changed to reflect the P&T Committee's decision. Drugs with an Include designation are then placed on the formulary and those with an Exclude designation are not placed on the formulary. Drugs given an Optional or Conditional Include designation are referred to the VAC for final formulary placement recommendation. If a Conditional Include drug is not placed on the formulary, a Prior Authorization program designating the clinical situations for which an individual patient may get the drug will be put in place.

The Express Scripts National P&T Committee consists of 19 non-employee physician members and one pharmacist member from active community and academic-based practices, representing a broad range of medical specialties. The Committee is chaired by an elected physician member. Four Express Scripts registered pharmacists, the medical

director, and the Chief Medical Officer offer staff support to the Committee. Although members receive reimbursement for travel costs and a stipend, their involvement on the P&T Committee reflects their desire to foster better patient care on a national level.

The following medical and pharmacy specialties are represented on Express Scripts' P&T Committee:

- Allergy & Asthma
- Cardiology
- Dermatology
- Endocrinology
- Family Medicine
- Gastroenterology
- Geriatrics
- Geriatric Pharmacy
- Infectious Disease
- Internal Medicine
- Neurology (Parkinson's & Dementia)
- Neurology (Seizures & Headaches)
- Obstetrics & Gynecology
- Oncology
- Ophthalmology
- Pediatrics
- Psychiatry
- Pulmonology
- Rheumatology

The committee is self-governing, establishing its own by-laws and policies and procedures, selects its own membership and elects its own chair.

3. Value Assessment Committee analyzes the Optional and Conditional Include pharmaceuticals. The Value Assessment Committee (VAC) considers the value of drugs by evaluating the cost of clinically comparable products. The VAC committee is comprised of Express Scripts' staff formulary management, research and product management, finance, and clinical account management. No members of the Value Assessment Committee serve in any capacity on the Therapeutic Assessment Committee. The VAC reviews drugs designated as Optional by the P&T Committee and develops a formulary-placement recommendation that is forwarded back to the Express Scripts National P&T Committee for review.

4. Review by Express Scripts National P&T Committee. As a final review, the actual formulary proposals are then returned from VAC to P&T to ensure that the overall structure and specific content are clinically appropriate.

Prescription drug costs have been increasing at double-digit rates due to inflation, increasing utilization, new drug introductions, and more sophisticated drug therapies. As a result, managing the pharmacy benefit has become an essential element of overall healthcare management. Left unmanaged, healthcare costs would rise at faster rates, with the likely ultimate result of reduced access and higher costs to consumers.

Affordable access to a clinically sound, high-quality pharmacy benefit depends on sophisticated, carefully constructed cost-control strategies — strategies that always place clinical value for patients first. The processes we use to develop our formularies for both biologic and non-biologic medications have been constructed to ensure that clinical considerations are paramount and fully taken into account *before* cost considerations.

In closing, thank you for the opportunity to testify before the Subcommittee on Health. Additionally, I appreciate the opportunity to respond to these follow up questions for the record.

Sincerely,

Ed Weisbart, MD, CPE, FAAFP

May 23, 2007

Janet Woodcock, M.D.
Deputy Commissioner, Chief Medical Officer
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Woodcock:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 2, 2007, at the hearing entitled "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Committee. In preparing your answers to these questions, please address your response to the Members who have submitted the questions and include the text of the Member's question along with your response. In the event you have been asked questions from more than one Member of the Committee, please begin the responses to each Member on a new page.

To facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Friday, June 1, 2007**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Melissa Sidman, Legislative Clerk/Public Health. An electronic version of your response should also be sent by e-mail to Ms. Melissa Sidman at **melissa.sidman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Anna G. Eshoo, Member
Subcommittee on Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

AUG 13 2007

Dear Chairman Dingell:

Thank you for the opportunity to testify at the May 2, 2007, hearing entitled, "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States," before the House Committee on Energy and Commerce, Subcommittee on Health. Janet Woodcock, M.D., Deputy Commissioner for Scientific and Medical Programs and Chief Medical Officer, testified on behalf of the Food and Drug Administration (FDA).

We are responding to the letter of May 23, 2007, you sent in follow-up to that hearing. As instructed in your letter, we have included FDA's responses to the questions asked by you and Representative Anna G. Eshoo on the following separate pages. Your questions are restated in bold font, followed by FDA's response.

Thank you again for the opportunity to testify. Please let us know if there are further questions.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Questions Submitted by the Honorable John D. Dingell

1. **Have any of the follow-on protein products approved under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act resulted in cost savings for consumers?**

Response: FDA cannot tell what the cost savings for consumers is because we have very little data comparing the prices of 505(b)(2) protein products with reference products.

2. **In your testimony, you gave examples of older, relatively simple protein products that the agency has approved under 505(b)(2). In both cases, you indicated that the Food and Drug Administration (FDA) required clinical data, and that FDA did not determine that these products were interchangeable with the reference products. Are you aware of any existing drugs on the market today for which 505(b)(2) "Biosimilar" products would be interchangeable and would not require clinical data for approval?**

Response: We expect that any application under section 505(b)(2) for a drug product that would be therapeutically equivalent to (substitutable for) a currently approved protein drug product would be required to contain clinical data for approval.

3. **Currently, two bills introduced in the House deal with the issue of biosimilars- H.R. 1956 and H.R. 1038. Please review each of these bills, and submit FDA's technical assessment of each bill, as well as how FDA would implement each bill if it were enacted. Please identify resource requirements, and any scientific, technical, or legal issues, in terms of how you would implement either of these bills, if enacted.**

Response: This question raises complex scientific and legal issues. We would be happy to meet with you and your staff to discuss them.

Questions Submitted by the Honorable Anna G. Eshoo

1. **The difficult debate over follow-on biologics is not unique to our country. The European Union has already dealt with this issue and created a pathway for approval of "biosimilars." Under the European system, innovators are granted up to 11 years data exclusivity, and each class of biologics is evaluated and tested according to guidelines developed after consultation and rulemaking by the European Agency for the Evaluation of Medical Products. Under this system, the follow-ons approved for marketing are required to undergo clinical testing. Is this the right model for the United States? How does this model compare to the bills that have been introduced so far?**

Response: The European Union's legislation is based on the principle that a "one size fits all" approach will not work for follow-on biologics due to their complexity and that the type and amount of pre-clinical and clinical data are determined on a case-by-case basis that is done by their regulatory agency (European Medicines Agency). FDA agrees that the amount and types of data needed to demonstrate safety and effectiveness will be influenced by a range of factors as noted in FDA's May 2, 2007, testimony. FDA has considerable experience with determining the data requirements for medical products, including subsequent versions of some protein products, and would determine the extent of clinical testing necessary to ensure that the product was safe and effective. In addition, FDA would be prepared to address scientific considerations related to the approval of follow-on biologics in a comprehensive manner through issuance of a series of guidances, as appropriate. FDA looks forward to working with Congress to ensure that any system developed meets the needs of the American people by promoting optimal development of safe and effective medical products and necessary protection of incentives for innovation.

2. **I have read some of the proposals that have been introduced to provide a pathway for follow-on biologics, and while I think the intent of these proposals is laudable, I am concerned about the specific language in some of these bills. One proposed statutory provision requires FDA to design clinical safety trials "to avoid duplicative and unethical clinical testing." To what extent does FDA conduct duplicative or unethical clinical testing?**

Response: FDA does not condone duplicative or unethical clinical testing in any setting.

3. **If a generic drug manufacturer were to submit an application for a follow-on version of a breakthrough cancer biologic, and that follow-on was not clinically tested: Would you be comfortable prescribing this follow-on to your patients? Would you be comfortable giving this follow-on to a member of your family?**

Response: FDA would not approve a follow-on biologic if the data submitted were not sufficient to establish that the follow-on product is sufficiently similar to an already approved product so that the Agency's finding of safety and effectiveness for the approved product may be relied upon, at least in part, to support the approval of the follow-on product.

Questions Submitted by the Honorable Anna G. Eshoo (cont.)

A major challenge in evaluating follow-on protein products is how much data, including clinical studies, will be necessary to show that a follow-on biologic is safe and effective. The data expected to be necessary to meet this standard will depend, among other things, upon the specific biological product at issue. In answer to your question, if FDA judged the data sufficient to support approval of a follow-on breakthrough cancer drug, then we would be comfortable with that product being prescribed in the appropriate clinical setting.

May 23, 2007

David Schenkein, M.D.
Vice President
Clinical Hematology/Oncology
Genentech
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Schenkein:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 2, 2007, at the hearing entitled "Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Committee. In preparing your answers to these questions, please address your response to the Members who have submitted the questions and include the text of the Member(s question along with your response. In the event you have been asked questions from more than one Member of the Committee, please begin the responses to each Member on a new page.

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Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226–2424.

Sincerely,

John D. Dingell
Chairman

RESPONSES TO QUESTIONS FROM MAY 2, 2007, HOUSE ENERGY & COMMERCE, HEALTH SUBCOMMITTEE HEARING, DR. DAVID SCHENKEIN, GENENTECH, INC.

THE HONORABLE EDOLPHUS TOWNS

A protein that was recently approved under the 505(b) 2 pathway, Omnitrope, contains a rating indicating that FDA has not evaluated sufficient data to justify a finding of interchangeability. In addition, you have recently testified it will take at least another ten years to establish standards of interchangeability for biological products. Since it appears that there is a huge gap in our understanding of how to demonstrate interchangeability of follow-on protein products, it might be advisable to allow physicians to make decisions based on their patients' specific clinical situations. Would you agree?

Yes. Given that follow-on versions of biological products cannot be identical to or the same as the innovator product they seek to emulate, only treating physicians should be allowed to make decisions regarding the interchangeability of products. They should not substitutable at the pharmacy level.

Given the greater complexities of biologics compared to smaller molecules, it seems logical that we establish a pre-approval requirement for clinical data with follow-on protein products.— Would you agree that, based on state-of-the-art science, FDA could not approve a follow-on protein product without clinical data?

Yes, I agree. Again, given the fact that follow-on biological products cannot be scientifically the same as the innovator product, it is necessary to test them independently in clinical trials to assure their safety and efficacy.

THE HONORABLE ANNA ESHOO

Representative Waxman's legislation provides no market exclusivity to innovator products—zero years. Representative Inslee's bill provides 14

years of market exclusivity. In the Senate, one of Senator Kennedy's draft proposals affords 10 years of market exclusivity to innovator products. For comparison, the European Union allows a total of 11 years of innovator exclusivity. In the U.S., pharmaceutical drugs (pills) are allowed 5 years of exclusivity plus 3 years for new uses of approved drugs under Hatch-Waxman.

What factors (e.g. expense, risk, length of Research and Development period, patent protections) must Congress take into account in arriving at the "right" number?

All of these factors need to be taken into consideration for Congress to arrive at the "right number." As you are aware, the research and development cycle of biological products is lengthy, costly and risky. In addition, given that the approval standard for a follow-on biologic will necessarily be based on "similarity" or "comparability" and not "sameness," we are concerned that the patent protections afforded innovators may not be sufficiently protective to ensure an adequate return on our investment. Specifically, follow on manufacturers may engineer around our patents, yet still gain FDA approval for a product that is "similar" or "close" to the innovator product. If this is the case, then follow on companies could theoretically piggy back on an innovator's investment once the innovator product goes to market. To ensure that companies such as Genentech are able to continue to invest in researching and developing life-saving therapies, Congress should construct a system that guarantees a sufficient amount of time during which our invention and data are protected. The legislative history of Hatch-Waxman indicates that Congress contemplated that 14 years is the intended period of effective patent life for a small molecule, whether achieved through patent protection, data exclusivity, patent term restoration, or a combination of all 3. As such, we believe that the same 14 years should be applicable to innovator biologics; however, the only true way to guarantee such time is through data exclusivity.

Genentech has 14 products on the market today. How important is market exclusivity for the average biotech company, which typically has only a few, if any, approved products in its portfolio?

Extremely important. Every company needs the assurance of an appropriate amount of time during which to recoup the investment made in R&D.

How does this system affect academic and medical research centers, such as Stanford University and the University of California, who are also patent holders? Any final bill must assure appropriate patent notification provisions to ensure that academic and medical research centers have sufficient notice in order to protect their own intellectual property rights. Without notification procedures, these institutions could unwittingly be denied the opportunity to protect their inventions, either through entering into licensing agreements or through litigation.

Assuring the safety and efficacy of all drugs is my #1 priority in this debate.

Why is it important for a follow-on manufacturer to conduct post-market studies to ensure the safety of their products?

Given that follow-on biologic products are, by definition, different than the innovator product, it is extremely important that the FDA have the authority to require post-marketing studies of the follow-on applicant in order to ensure the on-going safety of the product once it is marketed and available for use.

In constructing a follow-on biologics pathway, should Congress limit FDA's ability to impose post-market studies on follow-on biologics manufacturers?

No. The FDA should have the authority to require post-marketing studies of both follow-on and innovator companies.

If a generic drug manufacturer were to submit an application for a follow-on version of a breakthrough cancer biologic, and that follow-on was not clinically tested:

As a physician, would you be comfortable having your patients switched from a biological product that you have prescribed, to a follow-on product? Would you want your mother or child to receive a follow-on biologic?

No, I would not. Again, given that follow-on products are by definition different than the innovator they seek to replicate, it is critical that the follow-on product be independently tested to assure its safety and efficacy. As a physician, I would not prescribe a follow on product that had not been independently tested, as I could not be certain it was safe to do so.

What types of risks to patient safety does mandatory interchangeability present with respect to biologics? Do generic drugs (pills) possess these same risks?

There are significant risks to the patient in the context of mandatory interchangeability between follow-on and innovator products. Since the products are not identical, unlike small molecule generics, they should not be treated as such. Rather, only treating physicians should be empowered to make decisions about which drugs to prescribe his or her patients, whether a follow-on or innovator product. Generic pills (small molecules) are shown to be identical to their innovator counterpart. As such, the FDA is able to allow the safe interchangeability of generics in this context because the innovator counterpart has been proven to be safe and effective. In this case, the follow-on and innovator product cannot be the same and should be not deemed to be interchangeable by the FDA or a pharmacist. Only a treating physician should make such a determination.

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