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SAFE AND AFFORDABLE BIOTECH DRUGS: THE NEED FOR A GENERIC PATHWAY

HEARING

BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

MARCH 26, 2007

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SAFE AND AFFORDABLE BIOTECH DRUGS: THE NEED FOR A GENERIC PATHWAY

MONDAY, MARCH 26, 2007

HOUSE OF REPRESENTATIVES,
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 10 a.m., in room 2154, Rayburn House Office Building, Hon. Henry A. Waxman (chairman of the committee) presiding.

Present: Representatives Waxman, Kucinich, Davis of Illinois, Yarmuth, Norton, Van Hollen, Hodes, Welch, Davis of Virginia, Burton, Issa, Bilbray, and Sali.

Staff present: Phil Barnett, staff director and chief counsel; Kristin Amerling, general counsel; Karen Nelson, health policy director; Karen Lightfoot, communications director and senior policy advisor; Andy Schneider, chief health counsel; Sarah Despres, senior health counsel; Ann Witt, health counsel; Robin Appleberry and Rachel Sher, counsels; Earley Green, chief clerk; Teresa Coufal, deputy clerk; Caren Auchman, press assistant; Zhongrui "JR" Deng, chief information officer; Leneal Scott, information systems manager; Robin Pam, staff assistant; David Marin, minority staff director; Larry Halloran, minority deputy staff director; Jennifer Safavian, minority chief counsel for oversight and investigations; Susie Schulte, minority senior professional staff member; Kristina Husar, minority professional staff member; Patrick Lyden, minority parliamentarian and member services coordinator; Brian McNicoll, minority communications director; and Benjamin Chance, minority clerk.

Chairman WAXMAN. The meeting of the committee will please come to order.

More than 20 years ago the Congress enacted the Hatch-Waxman Act. That law has taught us three things: genetic drugs are good for patients, both medically and financially; with a little help, the market works, generic competition lowers drug prices; and generic competition does not bankrupt the brand name drug industry or slow innovation.

Maybe some big drug makers still dispute these lessons, but no one else does. But there is still no generic competition for one of the fastest-growing and most expensive categories of drugs, biologicals, those drugs produced from living cell cultures rather than from chemical synthesis.

Some of these drugs are near miracles for people with cancer, metabolic diseases, and immune disorders. They can stop disability and, in some cases, save lives. People need them. But some of these

drugs cost each patient tens of thousands of dollars a year. Some can cost hundreds of thousands per year. Many people cannot get access to these near miracles, and even when people can get them the prices drive up the cost of Medicare, Medicaid, and health insurance overall.

Why isn't the market helping? It is not because of the patent system that biologicals are protected from the competition that might lower prices. Biologicals, like other drugs, do enjoy patent protection. This allows manufacturers to enjoy a monopoly period during which they can get a significant return on their investments. But patents, or many of them, have already expired, and other patents are just about to expire.

And it is not the science of these drugs that protects them from competition. The technology is already here to make a safe and effective copy of some biotech drugs. Moreover, the technology is getting better every year, and we can make progress even faster if we allow companies to use it to make generics.

Instead, the monopoly on each of these drugs is perpetuated by the lack of a clear pathway for FDA to approve competing versions.

The Hatch-Waxman Act does not reach most of them. This costs all of us—taxpayers, insurance premium payers, and patients—billions of dollars. It also means that some very sick people simply cannot get the drugs they need.

I know that the science of these drugs is not simple. I take the questions of research, safety, and efficacy very seriously. The only way we can succeed in establishing robust competition for biotech drugs is with drugs the doctors and patients know they can count on, so we need to be sure that the FDA has the discretion to require the studies that are needed to establish that a copy of a biotech drug is equivalent to the brand name drug in safety and effectiveness. That is one of the things we hope to learn more about today.

But the big brand name companies have gone beyond legitimate concern and have thrown up a defensive smoke screen around biologicals. They say there will be problems of safety, decreased innovation, and limited savings. When discussing creating generic competition, they say things like, "Such action may also save consumers a few dollars here and there, although that is by no means assured, but whatever short-term savings may be achieved will come at an enormous long-term cost to the public. Focusing solely upon short-term, lower prices, a cheap drugs policy will inevitably reduce research and hinder our public health efforts."

Well, these arguments have a familiar ring to them. That is because the words I just read were the formal testimony that the Pharmaceutical Manufacturers Association gave to the House in 1983 when they were opposing Hatch-Waxman, and now manufacturers are using these same arguments again. But they were wrong then. Hatch-Waxman has saved patients billions of dollars and dramatically improved their access to drugs, and Hatch-Waxman did not reduce research or hinder public health.

And they are wrong now. A new path for FDA to approve generic biologicals will save patients billions in the future and will improve access to treatments and cures, and a new path will improve com-

petition, while preserving the market's strong incentive for research.

For the sake of patients, their families, public and private health insurance, and taxpayers, we must find a way to introduce competition to this market. When a patent expires, we owe it to consumers to find a way through competition to lower prices and still deliver a safe and effective product. When a patient expires, they no longer need the product, so the price will make no difference.

I look forward to the testimony of the witnesses today and learning more about the scope of the problem, the science, and the potential solutions.

[The prepared statement of Chairman Henry A. Waxman follows:]

Opening Statement of Rep. Henry A. Waxman, Chairman
Committee on Oversight and Government Reform
Hearing on "Safe and Affordable Biotech Drugs – The Need for a Generic Pathway"

March 26, 2007

More than twenty years ago, the Congress enacted the Hatch-Waxman Act.

That law has taught us three things:

- Generic drugs are good for patients—both medically and financially.
- With a little help, the market works: Generic competition lowers drug prices.
- And generic competition does not bankrupt the brand-name drug industry or slow innovation.

Maybe some big drug makers still dispute these lessons, but no one else does.

But there is still no generic competition for one of the fastest growing and most expensive categories of drugs—biologicals, those drugs produced from living cell cultures rather than from chemical synthesis. Some of these drugs are near-miracles for people with cancer, metabolic diseases, and immune disorders. They can stop disability and—in some cases—save life. People need them.

But some of these drugs cost each patient tens of thousands of dollars a year. Some can cost hundreds of thousands per year. Many people cannot get access to these near-miracles. And even when people can get them, the prices drive up the costs of Medicare, Medicaid, and health insurance overall.

Why isn't the market helping?

It is **not** because of the patent system that biologicals are protected from the competition that might lower prices. Biologicals, like other drugs, do enjoy patent protection. This allows manufacturers to enjoy a monopoly period during which they can get a significant return on their investments. But patents on many of them have already expired, and other patents are just about to expire.

And it is **not** the science of these drugs that protects them from competition. The technology is already here to make safe and effective copies of some biotech drugs. Moreover the technology is getting better every year, and we can make progress even faster if we allow companies to use it to make generics.

Instead, the monopoly on each of these drugs is perpetuated by the lack of a clear pathway for FDA to approve competing versions. The Hatch-Waxman Act does not reach most of them.

This costs all of us—taxpayers, insurance-premium payers, and patients—billions of dollars. It also means that some very sick people simply cannot get the drugs they need.

I know that the science of these drugs is not simple. I take the questions of research, safety, and efficacy very seriously. The only way we can succeed in establishing robust competition for biotech drugs is with drugs that doctors and patients know they can count on. So we need to be sure that the FDA has the discretion to require the studies that are needed to establish that a copy of a biotech drug is equivalent to the brand-name in safety and effectiveness. That's one of the things we hope to learn more about today.

But the big brand-name companies have gone beyond legitimate concern and have thrown up a defensive smoke screen around biologicals. They say there will be problems of safety, decreased innovation, and limited savings. When discussing creating generic competition, they say things like—and I quote:

> "[S]uch action may also save consumers a few dollars here and there, although that is by no means assured. But whatever short-term savings may be achieved will come at an enormous long-term cost to the public .... Focusing solely upon short term

lower prices—a 'cheap drugs' policy—will inevitable reduce research and hinder our public health efforts."[i]

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And they are wrong now. A new path for FDA to approve generic biologicals will save patients billions in the future and will improve access to treatments and cures. And a new path will improve competition, while preserving the market's strong incentives for research.

For the sake of patients, their families, public and private health insurance, and taxpayers, we must find a way to introduce competition to this market. When a patent expires, we owe it to consumers to find a way, through competition, to lower prices and still deliver a safe and effective product.

I look forward to the testimony of the witnesses today and learning more about the scope of the problem, the science, and the potential solutions.

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[i] House Committee on Energy and Commerce, Subcommittee on Health and the Environment, Statement of the Pharmaceutical Manufacturers Association, *Hearings on H.R. 3605: A Bill that Would Authorize the Food and Drug Administration to Approve Generic Copies of All Pioneer New Drugs,* 98th Cong. 127-131 (Jul. 29, 1983) (Ser. No. 98-67).

Chairman WAXMAN. Mr. Davis.

Mr. DAVIS OF VIRGINIA. Thank you, Mr. Chairman, for holding today's hearing to consider the implications of creating a regulatory pathway for approval of follow-on biologics. It is a very important subject, and certainly your leadership is appreciated and worthy of this committee's consideration.

Mr. Chairman, you have long been a leader in improving access to pharmaceutical drugs. Indeed, there is near universal agreement that the Hatch-Waxman Act has been extremely effective in allowing generic drugs to come to market and compete with brand name drugs. This competition has benefited countless citizens, as well as the Federal Government, by using natural market economics to bring down the price of prescription medicine. You are to be commended for your leadership in improving access to these life-saving medications.

It is my understanding you have recently introduced legislation that would, in fact, create a regulatory pathway for the FDA to approve follow-on biologics. We have been reviewing the legislation with interest, and we expect it will inform today's discussion.

I look forward to exploring your proposal further. For now, let me just offer a few preliminary thoughts on this very complex subject.

The first principle guiding this effort should be to foster innovation and the discovery of new cures. After all, there is no new therapeutic, by definition there can be no follow-on. Accordingly, we need to protect the intellectual property of innovative firms. Given the high cost of research, development, manufacturing, and regulatory approvals, IP protections are clearly a critical factor for biotech startups when they are securing venture capital and pursuing partnerships with larger firms.

Today we will hear from economist Henry Grabowski, who will explain that increased patent uncertainty and IP litigation would have a significant negative effect on capital market decisions for emerging private and public biotech firms. He will explain that if the Federal Government either weakens patent protections or increases the chance of litigation there will likely be a corresponding decrease in investment, and therefore less research and development of biologics. It would be tragic if legislation intended to increase access to medicine would have the unintended result of stifling innovation, preventing the discovery of cures of presently terminal diseases.

I hope you would agree with me, Mr. Chairman, about the importance of fostering a vibrant and innovative culture where we encourage our brightest minds and daring entrepreneurs to do the research, provide the investment so that we may some day discover the cure for cancer or Lou Gehrig's disease.

Reflecting on the Hatch-Waxman Act, you got it right when you recognized the importance of balancing the twin goals of bringing generic drugs to market while at the same time leaving intact the financial incentive for research and development.

One of the keys to this successful balance in that legislation was the guarantee of 5 years of market exclusivity for innovative companies. Incidentally, European Union regulators currently provide 10 years of market exclusivity for European drugs for innovative

drugs. Some amount of market exclusivity for the innovator is necessary under any regulatory pathway for follow-on biologics.

The second imperative is to provide a mechanism so the FDA is able to guarantee the safety and efficacy of follow-on biologics. To do so we have to recognize the fundamental differences between biologics and chemical-based pharmaceuticals. What has proven to be successful in the case of traditional drugs is not necessary transferrable to the science of biologics. For instance, it is currently possible to know the complete character of a small molecule drug. This knowledge enables the FDA to approve generic drugs with the same characteristics as the innovator drug without requiring generic companies to test and prove the drug's efficacy and safety again. However, current science has not advanced sufficiently to give us the same confidence that a follow-on biologic is identical to a previously approved biologic based on molecular structure, alone.

Unlike traditional drugs, which are chemically based, biologics are made from living organisms. Even minor variations in manufacturing processes can have a significant impact on the final character and consistency of the biologic and its effect on the human body.

This diagram on the board comparing a biologic used to treat anemia and a traditional drug that treats peptic ulcers disease demonstrates the difference between traditional chemical drugs and biological therapies. As you can see, the biologic is significantly more complex than a traditional drug, having a molecular weight of 30,000 versus 351. This is a critical distinction between traditional generic drugs and follow-on biologics. Any regulatory pathway must take full account of this distinction, which for now seems to point to the inescapable conclusion that clinical trials on some level will be essential to ensure the safety and efficacy of follow-on biological products.

Again I want to thank you, Mr. Chairman, for spurring a discussion on this important subject. I look forward to hearing from our distinguished panel of witnesses.

[The prepared statement of Hon. Tom Davis follows:]

Statement of Rep. Tom Davis
Ranking Republican Member
Committee on Oversight and Government Reform
Safe and Affordable Biotech Drugs – The Need for a Generic Pathway
March 26, 2007

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It is my understanding that you have recently introduced legislation which would in fact create a regulatory pathway for FDA to approve follow-on biologics. We have been reviewing your legislation with interest, as we expect it will inform today's discussion. I look forward to exploring your proposal further.

For now, let me just offer a few preliminary thoughts on this complex subject.

The first principal guiding this effort should be to foster innovation and the discovery of new cures. After all, if there is no new therapeutic, by definition, there can be no follow- on. Accordingly, we need to protect the intellectual property (IP) of innovator firms. Given the high cost of research, development, manufacturing, and regulatory hurdles, IP protections are clearly an important factor for bio-tech start-ups when they are securing venture capital and pursuing partnerships with larger firms. Today, we will hear from economist Henry Grabowski who will explain that increased patent uncertainty and IP litigation would have a significant and negative effect on capital market decisions for emerging private and public biotech firms. He will explain that if the federal government either weakens patent protections or increases the chance of litigation, there will likely be a corresponding decrease in investment and therefore less research and development of biologics.

It would be tragic if legislation intended to increase access to medicine would have the unintended result of stifling innovation, preventing the discovery of cures for presently terminal diseases.

I hope that you would agree with me, Mr. Chairman, about the importance of fostering a vibrant and innovative culture, where we encourage our brightest minds and daring entrepreneurs to do the research and provide the investment, so that we may some day discover the cure for cancer or Lou Gehrig's disease.

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intact the financial incentive for research and development. One of the keys to this successful balance in that legislation was the guarantee of five years of market exclusivity for innovator companies. Incidentally, European Union regulators currently provide 10 years of market exclusivity for innovator drugs. Some amount of market exclusivity for the innovator is necessary under any regulatory pathway for follow-on biologics.

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For instance, it is currently possible to know the complete character of a small-molecule drug. This knowledge enables the FDA to approve generic drugs with the same characteristics as the innovator drug, without requiring the generic company to test and prove the drug's efficacy and safety again. However, current science has not advanced sufficiently to give us the same confidence that a follow-on biologic is identical to a previously approved biologic based on molecular structure alone. Unlike traditional drugs, which are chemically based, biologics are made from living organisms. Even minor variations in manufacturing processes can have a significant impact on the final character and consistency of the biologic and its effect on the human body.

[reference slide here] This diagram comparing a biologic used to treat anemia, and a traditional drug that treats peptic ulcer disease, demonstrates the differences between traditional chemical drugs and biologic therapies. As you can see, the biologic is

significantly more complex than a traditional drug, having a molecular weight of 30,000 vs. 351.

This is a critical distinction between traditional generic drugs and follow-on biologics. Any regulatory pathway must take full account of this distinction, which for now seems to point to the inescapable conclusion that clinical trials on some level will be essential to ensure the safety and efficacy of follow-on biologic products.

With that, I want to thank you again for spurring a discussion on this important subject. I look forward to hearing from our distinguished panel of witnesses.

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

Without objection, all Members will be permitted to enter an opening statement in the record. Do any Members wish, however, to make any comments before we hear from our 15 witnesses? Mr. Issa.

Mr. ISSA. Thank you, Mr. Chairman. I will be brief. I will put my formal statement in the record, particularly because it sounds an awful lot like Mr. Davis'. The view is somewhat the same, and that is that it is very clear that we know a great deal about chemical compounds and we can say a chemical is a chemical, but, for example, Mr. Chairman, would you want to have these two oranges substituted as though there were no difference? Would you accept that a Florida orange is the same as a California orange if you have to peel it, Mr. Chairman? And, for Mr. Sali who is not here today, do you really think that any Russett potato is an Idaho potato and should be interchanged and have no value, no second testing of whether or not it makes a good french fry?

Now, clearly we know how to make grain alcohol, and if I am buying grain alcohol, Mr. Chairman, it is very clear that I know that it is alcohol plus about 3 percent water that just gets in if you get the air to it. But, Mr. Chairman, do you really think that a $90 bottle of California wine that says Merlot is equal to this fine boxed Merlot? And would you want to go to the dinner table or the hospital and have them interchanged without your prior approval, or perhaps a little taste?

This is biologics. These are made by process. Mr. Chairman, they may both be a Merlot, but as a Californian, I am sure that you would not want them interchanged without your prior approval.

With that, I yield back.

[The prepared statement of Hon. Darrell E. Issa follows:]

March 26, 2007

Opening statement of Rep. Darrell Issa for full committee hearing on "Safe and Affordable Biotech Drugs - The Need for a Generic Pathway"

Thank you, Mr. Chairman and Ranking Member Davis, for holding this important hearing on the safety of biological products. I would also like to thank the witnesses for taking time out of their schedules to testify today.

The medicines that make it to patients undergo years of research and development to prove they are safe and effective. The lucky few products that do make it to approval have gotten there as a result of hundreds of millions or even billions in investment. This is especially true for complex biologic medicines. These miracles of modern medicine are proteins grown in living cells which have helped millions of Americans who suffer from a wide variety of diseases. I'm proud to say that my home state of California is home to many of these cutting-edge biotechnology companies who are working on innovative cures and treatments for patients.

Access to, and affordability of, these biotech drugs are both extremely important. But if we cannot guarantee the efficacy, and more importantly, the safety of follow-on biologics, we cannot allow them to be produced for consumer use.

Many have compared the production of follow-on biologics to the production of generic drugs. But there are many differences that make simply modeling the approval process of follow-on biologics after that for generic drugs unsafe and unacceptable.

Generic drugs can be approved after the generic applicant shows that the drug is the bioequivalent of the original, or innovator, drug and that it contains the same active ingredient. But unlike generic drugs, it is as yet impossible to demonstrate that a follow-on biologic is identical to a pre-approved innovator product. The existing generic drug approval process does not require clinical trials. But because the complexity of the structure of biologics is greater than that of small molecule drugs, an abbreviated approval process without clinical trials cannot ensure the safety or efficacy of follow-on biologics.

Additionally, the very nature of biologics makes them unsuitable to be manufactured without significant FDA oversight. Biologics are living organisms and as a result, any variation in manufacturing process, however minor, can drastically change the way they function in the body. Biologics can elicit immune responses which can render the product ineffective. Europe's experience with follow-on biologics demonstrates that some of these immune responses can be life-threatening. Clinical trials are essential and must be required to ensure that follow-on biologics are as safe and effective as the

innovator product they are trying to copy. Furthermore, follow-on biologics should not be allowed to be marketed under the same name as the innovator. According to the FDA, there is no scientific basis to conclude that such products are interchangeable. Patient safety cannot be guaranteed if the full and proper FDA approval process is not followed.

To illustrate the difference between innovator biologics and follow-ons, take the differences between various brands of wine as an example. Using grapes from the same grower, wineries in different climates or those using different processes will produce a Cabernet of varying quality. The type of barrels, time of fermentation, and a number of other factors play into this equation. This is extremely analogous to manufacturing a biologic. The difference between the two, however, is that when you drink from a bottle of bad wine you aren't likely to elicit a severe immune response. This is not the case with a defective biologic, and we cannot take these safety concerns lightly.

In addition to safety concerns, we also need to continue to foster an environment of innovation here in the United States. Innovator companies spend hundreds of millions of dollars to research and develop biologics – many, if not most, do not make it to market or recoup their investment. I believe that a balance can be achieved between consumer access and savings, and providing incentives for innovators to take the investment risks to create tomorrow's life-saving new cures and treatments. I hope that biotech companies will be able to continue to invest in uncertain, but rewarding, research and development, and have many more promising therapies available to patients in the years to come.

Thank you Mr. Chairman. I look forward to hearing from the witnesses and further discussing the safety of follow-on biologics.

Chairman WAXMAN. Mr. Davis.

Mr. DAVIS OF ILLINOIS. Yes, Mr. Chairman, I would like to make a brief statement.

Chairman WAXMAN. Before I recognize you for that purpose, I would like to inquire if you have any props. [Laughter.]

The gentleman is recognized.

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman. I shall, indeed, be brief. But first of all let me thank you for calling this hearing.

In 1984 the landmark Hatch-Waxman Act provided a cost-effective alternative to branded drugs with the creation of a traditional generic pharmaceutical industry. Today's hearing marks yet another landmark as we are being called upon to address escalating biopharmaceutical costs.

This issue is near and dear to me, one, as a former health administrator, but also because my congressional district has more hospitals and more hospital beds than any other congressional district in the country. Illinois has about 200 hospitals, most of them nonprofit. State hospitals are losing money, and another third are barely breaking even, notwithstanding cuts in Medicare and Medicaid.

According to Crane's Chicago Business, on February 13, 2006, while the State of Illinois has implemented prescription drug assistance programs like the Senior Care Pharmaceutical Program, State Pharmaceutical Assistance Plan, All Kids Program that provides health insurance coverage and prescription drugs to children across all socio-economic groups, they help to buffer costs.

However, the sad reality is that cuts in Federal spending tend to shift costs to insured patients and their employers. By definition, health care is eating up a piece of our income, which is especially bad news for the 26 percent of Chicagoans, including 164,203 with full-time jobs and 43,876 with at least a college education who lack health insurance. These data are particularly disturbing when you take into consideration the median household income for Chicago is $38,625 a year.

With this in mind, I welcome today's distinguished panelists and look forward to their insight and recommendations on how we can buildupon the foundation of generic competition for our consumers laid some 23 years ago under the Hatch-Waxman Act toward the attainment of a pathway to safe and affordable biotech drugs.

I guess if I was to have any kind of prop, I'd just take this water, which is pretty pure, and be delighted to have it.

Again, thank you, Mr. Chairman, for having this hearing.

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

Does any other Member wish to be recognized for an opening statement? Mr. Yarmuth.

Mr. YARMUTH. Mr. Chairman, two things real briefly. First of all, I hope that Mr. Issa would accept an amendment to his list in saying that no self-respecting Kentuckian would accept Tennessee sour mash whiskey for a Kentucky bourbon.

Mr. ISSA. Now that is bipartisan if I ever saw it.

Mr. YARMUTH. Thank you.

Also, I would like to say that I think the chairman and Mr. Davis have very accurately expressed and illuminated the conflicting issues that we have to deal with on this topic.

I would also mention the fact that we have to recognize that much of the research that leads to the development of these drugs and these medications, both pharmaceutical and also these biologics, are funded by taxpayer dollars initially, so that we have an overriding mandate to do what is best for the taxpayer, who is paying for most of this research at the very foundational levels.

Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you very much.

We will now hear from our witnesses today. Our first witness I am pleased to welcome is Dr. Janet Woodcock. She is the Deputy Commissioner for Operations and Chief Medical Officer of the Food and Drug Administration.

Since you are standing, I will have you continue to stand because it is the practice of this committee to put all witnesses under oath.

[Witness sworn.]

Chairman WAXMAN. The record will indicate that you answered in the affirmative.

We are delighted to have you here. We will put your full statement in the record. If it is possible, we would like to ask you to keep to around 5 minutes.

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

Dr. WOODCOCK. Thank you. Mr. Chairman and members of the committee, I am Janet Woodcock, Deputy Commissioner and Chief Medical Officer of the Food and Drug Administration. I 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 relied not only on my experience leading the Center for Drug Evaluation and Research for over a decade, but also on my 8 years of experience working in the Center for Biologics Evaluation and Research [CBER]. While in CBER I served as Acting Deputy Center Director and as 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 generic drugs 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. They constitute about 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.

The success of the program has stimulated competition. For the last decade, the rate of submission to the Office of Generic Drugs has rapidly increased. Submissions doubled between 2002 and 2006, to a current rate of about 793 applications per year.

The office has implemented numerous process improvements, have improved increased efficiency of the review process, and recently, as part of FDA's initiative on pharmaceutical quality for the

21st century, OGD instituted the question-based review. Eventually it is hoped this change will decrease submission of manufacturing supplements by about 80 percent, and thus free up more time of the reviewers to deal with this increased submission rate.

While the generics program has been very successful for small molecules, scientific challenges remain. We do not have good bioequivalents methods for inhaled or many topical medications, and must require clinical trials to demonstrate equivalence. This has inhibited consumer access to generic versions of these types of products.

In addition, a number of drugs are made from complex molecules. In these cases, it can be difficult to tell whether a proposed generic version is structurally identical to the innovator product.

Recently, as part of its critical path initiative, FDA has been evaluating the science needed to address these issues for generic drugs and is planning to lay out the scientific research that is needed to improve the process, as we did a number of years ago for innovator medical products.

The topic for discussion today is variously referred to as follow-on proteins, follow-on biologics, generic biologics, as well as other labels. Many of these terms are very imprecise and confusing, and I hope we can discuss terminology.

Largely, these terms are intended to refer to biotechnology produced protein products. In the United States, such products are regulated either as drugs under the Food, Drug, and Cosmetic Act, or as biologic products under the Public Health Service Act. Whether regulated as drugs or biologic products, proteins fit into the category of complex molecules that can be difficult to fully characterize.

Copies of protection products that are regulated as drugs may be considered for the abbreviated applications pathways that exist under section 505. The very simplest peptide products may be able to demonstrate that they contain the same active ingredient as the innovator product, and thus may be considered under 505(j), what is commonly regarded as the generic drug pathway.

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

The degree to which any abbreviated pathway could be used for any given protein depends on many factors, including its physical complexity, the availability of functional assays to characterize it, and its clinical use.

An abbreviated pathway does not exist for copies of protein products approved under the PHS Act. FDA has approved several follow-on proteins under 505(b)(2), including a recombinant hyaluronidase and recombinant version of human growth hormone.

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

I will be pleased to answer your questions regarding these complex issues.

[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

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

UNITED STATES HOUSE OF REPRESENTATIVES

"FOLLOW-ON PROTEIN PRODUCTS"

March 26, 2007

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Committee, 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. Finally, it is recognized that 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)), but the Agency has approved a number of biological products, such as human growth hormone, under the FD&C Act.

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. Because these terms are imprecise and can be confusing, and because the use of the term *generic* inaccurately implies the same meaning as exists for generic drugs, I will try to rely instead on terms with established meanings or definitions.

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 microorganisms, 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 CDER under the FD&C Act as drugs (e.g., hormones such as insulin and human growth hormone), and others were regulated by 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. 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, often 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 its 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 additional data necessary, other than the underlying clinical data supporting the approved product, 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 the *same* as an approved product, the very nature of protein products makes comparisons of one protein to another, including 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.

[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.

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 nonclinical and clinical data are necessary to establish that the proposed product is safe and effective. FDA 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 is the situation in which a manufacturer has sought to demonstrate that a new version of its licensed biological product manufactured using a different manufacturing process is comparable to the product manufactured using the original process. Another example 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). Typically, demonstrating the similarity of a follow-on protein product to a reference product will 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 may be currently 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 is well understood. In the case of other products, the primary mode 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 it 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 it 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.

The Agency 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 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.

Chairman WAXMAN. Thank you very much, Dr. Woodcock.

As you mention in your testimony, for over 10 years FDA has allowed brand name manufacturers of biotech drugs to make certain changes in the process by which they manufacture their products, but without repeating all the original clinical trials, under something called comparability protocols. I am interested in understanding the scientific rationale for allowing brand name manufacturers to make process changes without new clinical trials. I am also interested in its applicability to follow-on and biogeneric products.

What was the scientific basis for FDA's conclusion that clinical outcome trials are not necessary to assess the effects of certain biological product changes?

Dr. WOODCOCK. Manufacturing changes and process changes are undertaken for all pharmaceutical products, whether drugs or biologics. In each case we have to determine whether or not the change could result in any clinically significant change in the product, whether it is a small molecule or whether it is a large, complex molecule of some kind. FDA has a long history of quality regulation, putting into place procedures, both physical characterization of the new product and comparing it to the old product, functional characterization of a new product compared to the original product, and sometimes clinical characterization of a new product. It depends on, as I said in my oral testimony, how much science we have available to assess these changes.

If we can be sure, based on a structural characterization, which we often can for a drug, then that would be sufficient for a small molecule drug. If that structural characterization isn't enough to assure that the new version is similar to the old version, then other types of tests might be necessary. And in some cases we might even require clinical tests.

For example, with small molecule drugs, when the formulation is changed we may require new bioequivalent studies.

Chairman WAXMAN. So that is completely within your discretion based on whether you think it is appropriate to have further evaluations, further studies?

Dr. WOODCOCK. Yes. There are multiple scientific issues that come into play in any given manufacturing change.

Chairman WAXMAN. I know most of these comparability decisions involving biotech drugs or any other drugs are confidential, but with the biotech drug Avonex the information is public. I assume you are familiar with that case?

Dr. WOODCOCK. Yes.

Chairman WAXMAN. What kinds of process changes did FDA permit in that case without repeating the original safety and effectiveness trials?

Dr. WOODCOCK. In that case the original cell line that had been used to manufacture the product that was used in the clinical trials was no longer available, so the manufacturer had to go back and redo all of that and duplicate the manufacturing process that had been used for the original product. That is well described publicly. They made some original attempts. Those weren't successful.

They made some subsequent attempts and then an extensive number of comparisons were made between the original product and the second version of the product, both the kinds I just de-

scribed, both physical/chemical comparisons, functional comparisons, and so forth, so that at the end of the day it was decided that the products were similar enough that FDA could extrapolate from the clinical data that was derived for the first product to the new product.

Chairman WAXMAN. Were the changes between the two products significant?

Dr. WOODCOCK. The products were very similar, ended up being very similar.

Chairman WAXMAN. I meant the process changes. Were they significant?

Dr. WOODCOCK. The manufacturer attempted to duplicate the similar process that was originally done with the first product, but it was in a different site, in a different scale, and so forth, so there were differences. It was not the identical cell line. It wasn't the identical product that had been made, and so forth.

Chairman WAXMAN. Are these changes similar to the kinds of changes that might be required to manufacture a follow-on product?

Dr. WOODCOCK. The difference between that example and the instance where a new manufacturer would attempt to manufacture a follow-on product would be that in the Avonex case. The manufacturer had access to all the information about the process of manufacturing the first product. That is very important information, because it has information on all the intermediate steps and what happens during the manufacturing and purification process, and so on.

Chairman WAXMAN. Thank you.

Mr. Davis.

Mr. DAVIS OF VIRGINIA. We will start with Mr. Issa.

Chairman WAXMAN. Mr. Issa.

Mr. ISSA. Thank you. Thank you, Mr. Chairman, and thank you, Ranking Member Davis.

Avonex appears to be an example sort of—I will use a different wine than the one here, but you are talking if the Rothschilds trying to duplicate after they have had to clear their grapes away and put a new crop in. You have the same maker with the same wine masters—in this case scientists—trying to duplicate what they had already made. Is that roughly correct? You may not be a California wine drinker, so I know it can be challenging.

Dr. WOODCOCK. I love California wine.

Mr. ISSA. You won't love the one here in this box. Trust me.

Dr. WOODCOCK. Yes. As an analogy, that is quite reasonable.

Mr. ISSA. OK. So the next step that the chairman's legislation or the legislation we are hearing here today would attempt to do is to say that, even though you had to sort of teach or go through a process, a re-learning process, even with the original designer, you are going to try and transfer this to a different winery, and they are going to try to set up, but they are not going to have the right to every trade secret, if you will. Not every nuance of the process is, in fact, in the public domain. Is that correct?

Dr. WOODCOCK. That is correct. We face that now with our generic drug program.

Mr. ISSA. OK. And you mentioned earlier that you have had chemical equivalents that didn't work out so well when they went generic, so to speak, even among name manufacturers. When an insurance company does a formulary and says this is equal to this, that is not always right, is it? There are side effects that are unanticipated often?

Dr. WOODCOCK. The generic drugs that we approve are fully interchangeable with the innovator drugs. They are therapeutically equivalent.

Mr. ISSA. You have never had a side effect?

Dr. WOODCOCK. We have numerous reports of side effects; however, we investigate those and we have extraordinarily rarely found any instance where there would be therapeutic inequivalence between a generic drug and an innovator drug.

Mr. ISSA. Now, when we get to biological and follow-on immune problems that occur, that is a different problem that you are not presently seeing as much in small cells but you do see it in biologics, don't you?

Dr. WOODCOCK. Yes. Proteins are what is called immunogenic. They produce often an immune response in people when they are administered.

Mr. ISSA. So if there are two otherwise the same biologies, the original and the follow-on, one could very much have a different immune response that would lead somebody who had successfully fought a disease to somehow develop a resistance; is that correct?

Dr. WOODCOCK. The immune response to a protein can cause many things. It can cause what you just said, which is neutralizing the effect, the beneficial effect of the protein.

Mr. ISSA. And then you could find yourself unable to deal with either drug. In other words, you could make that change and find yourself opted out of the cure or the treatment?

Dr. WOODCOCK. That is true, and there are difficulties, for example, with insulin sometimes.

Mr. ISSA. So, given that you have this history, wouldn't, in the case of follow-on biologics, at least until this problem can be quantified, wouldn't you have a bias, an almost exclusive bias toward clinical trials, even if we gave you the jurisdiction and the right to shortcut those, limit those, eliminate them? From a standpoint of unsettled science, wouldn't it be proper to have clinical trials to ensure that is not happening when, in fact, it can take someone who is surviving and put them in a position where they can no longer survive?

Dr. WOODCOCK. Currently—and, of course, I can only address the proteins that we are looking at under the 505, under the FD&C Act.

Mr. ISSA. Right, and you admit those are, by definition, less likely to be unknowns than the ones we are going toward; is that right?

Dr. WOODCOCK. No. That is where the terminology I think is very confusing. We have approved proteins under the Food, Drug and Cosmetic Act provisions under 505(b)(2), and in those cases, for those recombinant proteins we have looked at the immunogenicity in people.

Mr. ISSA. OK, but you have looked at them?

Dr. WOODCOCK. Yes.

Mr. ISSA. So, again, my one final exit question here in this short time: clinical trials are the only way to know whether substantially similar, substantially identical follow-on biologics are, in fact, going to have differences in the immune response, or whatever term is appropriate; is that right?

Dr. WOODCOCK. Yes. We have a very limited understanding of the basis of an immune response, and we are not able to fully predict immunogenicity in humans right now from non-clinical data.

Mr. ISSA. And this could be dangerous?

Dr. WOODCOCK. The immunogenicity must be evaluated.

Mr. ISSA. Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you, Mr. Issa.

Mr. Yarmuth.

Mr. YARMUTH. Thank you, Mr. Chairman.

Dr. Woodcock, some in the brand name industry argue that any process for approving copies of biologics should follow the European Union model. The EU's governing directive, which is comparable to a statute, is extremely flexible and gives regulators great discretion to set procedures and standards and so forth.

The drug regulatory body there, the EMEA, has also established very particular procedures and approval standards to implement those directives. You are nodding, so you are obviously familiar with that process or that model?

Dr. WOODCOCK. Yes.

Mr. YARMUTH. And the biotech industry seems to like that public process that is used there for establishing and setting guidelines that contain the data requirements for biosimilars because the data gathering process allows those companies to help dictate what data their competitors must produce, and, of course, that would take a lengthy period of time.

Is the FDA required to undertake a public process for establishing data requirements?

Dr. WOODCOCK. No. We are not required to.

Mr. YARMUTH. Do you think it is scientifically necessary for FDA to engage in a public guideline process to establish the data requirements for a follow-on protein product?

Dr. WOODCOCK. What FDA does currently is engage with the manufacturer in discussions—of course, those are not public—to provide advice on any manufacturer interested in pursuing a follow-on under the 505(b)(2) process. But we often write scientific guidance for manufacturers because it provides better predictability and it provides, as you said, transparency.

We are in the process of writing overall guidance on the process of scientific approach to follow-on proteins under 505(b)(2).

Mr. YARMUTH. Do you think that the process the European Union uses, if we adopted that system here, would have the effect of freezing science at all? Is that a risk in doing that?

Dr. WOODCOCK. I am really not able to comment on that.

Mr. YARMUTH. Thank you, Mr. Chairman. I yield back.

Chairman WAXMAN. The gentleman has a couple minutes, would you yield your time to me?

Mr. YARMUTH. I would be happy to yield my time to the distinguished chairman.

Chairman WAXMAN. Thank you.

I just wanted to point out that the questioning by my colleague, Mr. Issa, about how you might need to have clinical trials to understand possible concerns, that is legitimate. FDA does now at the present time allow some changes in the process without requiring clinical trials, but I do want to point out that the legislation that I have introduced would allow FDA to decide, when they think clinical trials are appropriate, to require clinical trials.

I do want to ask you this. In the use of comparability protocols limited to simple proteins, can the manufactures of more complex proteins make changes in their products without repeating the original clinical trials?

Dr. WOODCOCK. Yes, they can, if the science is there. It is very desirable for manufacturers of pharmaceuticals of any kind to make continuous improvements in their manufacturing process to maintain the quality of the pharmaceuticals as soon as possible and the efficiency of the process as good as scientifically possible. So FDA has adopted procedures, as I said, that allow manufacturers to make changes to their manufacturing process or perhaps open up new plants, say, if there is a demand for the product, and the amount of data that has to be generated really depends on the complexity of the product, how well we can physically characterize the product, and how confident we are that physical characterization will extrapolate to the same performance. But we may require many additional steps, up to and including clinical studies now, particularly of immunogenicity.

Chairman WAXMAN. Well, do you and other FDA scientists feel confident that comparability assessments provide adequate protection to patients from unsafe or ineffective biotech drugs?

Dr. WOODCOCK. The comparability assessment puts the burden on the manufacturer. The manufacturer must show to FDA's satisfaction that the change has not introduced anything that would be detrimental to the clinical performance of the drug. So how much evidence is needed after a manufacturing change depends on how well the manufacturer can demonstrate that product is going to perform the exact same way as the original product did in the clinical testing.

Chairman WAXMAN. And as science evolves, you will know better whether the comparability requires clinical tests or not; is that correct?

Dr. WOODCOCK. The ability to physically characterize protein molecules and other complex substances has evolved and is continuing to evolve, and so over time we are going to be able to do a better and better job of controlling the quality of these products and allowing for continuous improvement.

Chairman WAXMAN. Thank you very much.

Mr. Davis.

Mr. DAVIS OF VIRGINIA. I finally have my comparison up there. We talked before about how complex these are. This diagram up there, as you see, compares a biologic used to treat anemia and a traditional drug that treats peptic ulcers. It demonstrates the difference between the traditional chemical drugs and biological therapies.

Dr. WOODCOCK. Yes.

Mr. DAVIS OF VIRGINIA. As you can note on this, the biologic is significantly more complex than a traditional drug.

Dr. Woodcock, you highlight in your testimony the importance of ensuring that facilitating the development of follow-on products through abbreviated pathways doesn't discourage innovation and the development of new biological products, and you refer to Hatch-Waxman as a balanced approach. Do you think an extended period of data exclusivity as well as certain patent protections like Hatch-Waxman would help encourage innovation and development with biological products?

Dr. WOODCOCK. Sir, I am a doctor and a scientist, and that is really outside of my area of expertise.

Mr. DAVIS OF VIRGINIA. OK, so you don't want to make the economic or policy determinations on that?

Dr. WOODCOCK. No.

Mr. DAVIS OF VIRGINIA. OK. You also state in your testimony that demonstrating the similarity of a follow-on protein product to a reference product is more complex and would require new data. Does this mean FDA would require clinical safety data for follow-on biologics?

Dr. WOODCOCK. There is a very large range of complexity. All right? The erythropoietin molecule that you have here is a pretty complex example. There are very, very small biologic drugs of different kinds. So the amount of assurance and the amount of data that would be needed is really based on how complex something is and how well it can be characterized in different ways.

Mr. DAVIS OF VIRGINIA. But a slight alteration could have, you know, significant clinical manifestations, wouldn't it?

Dr. WOODCOCK. FDA would not approve a follow-on product or a generic drug that we were not confident would have the same performance as the innovator drug.

Mr. DAVIS OF VIRGINIA. What level of clinical safety data would be necessary for approval, ball park?

Dr. WOODCOCK. Well, to talk about this we have to get into terminology a little bit. Please bear with me.

The abbreviated application process for 505(b)(2), for example, may rely on some fact of the approval of a prior product. All right?

Mr. DAVIS OF VIRGINIA. Yes.

Dr. WOODCOCK. But we may approve a product using an abbreviated application where some of the data, maybe some of the clinical trials or animal studies do not have to be repeated. However, that resulting of proof product is not considered substitutable for the other product. In other words, each of them stand alone and they can't be switched at the pharmacy, or it is not recommended they would be. That is one level.

Another level would be for a manufacturer to seek interchangeability, full interchangeability. So far the proteins that we have approved all stand on their own. They have had abbreviated applications but they are not considered interchangeable with any of the other proteins in that class. For example, human growth hormone or hyaluronidase.

Mr. DAVIS OF VIRGINIA. You testified that the science and technology isn't sufficiently advanced to allow for comparison of com-

plex protein products. How close are we to discovering those technology methods; 5 years; 10 years?

Dr. WOODCOCK. It is going to be a continuum, and right now we are very short peptides, which are as small as the ranidine molecule you are showing there, for example, or in the same ball park. We can do it now, but those are very, very small compared to the erythropoietin molecule, so it is going to be a step-wise progression over a decade or so.

Mr. DAVIS OF VIRGINIA. Are there any non-clinical tests or technology that could fully substitute for studying the safety of biotech products in humans?

Dr. WOODCOCK. As I said, right now we do not have the science around the immune system to adequately predict the human immune response fully to any given product.

Mr. DAVIS OF VIRGINIA. You listed two examples, omnitrope and—I can't pronounce the other one. Hyaluronidase?

Dr. WOODCOCK. That is pretty good.

Mr. DAVIS OF VIRGINIA. Neither was rated by FDA as therapeutically equivalent or substitutes for other biologics on the market. Many believe interchangeability or substitution is where the most cost savings would occur. Of course, the balance here is safety versus efficiency and speed to market.

When do you think the FDA will be able to rate a biologic product as interchangeable? And do you think the FDA needs this authority if the science isn't developed yet?

Dr. WOODCOCK. For the 505(b)(2) drugs, which is what I can comment on, manufacturers would need to do additional clinical studies that would demonstrate interchangeability, and that is a further step. That is a higher bar than simply getting on the market, an abbreviated application. Does that make sense to you?

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Welch.

Mr. WELCH. Thank you, Mr. Chairman.

Some of the drug companies have said that when a biotech product is derived from a specific cell line, any copy of the product will have to begin with a different cell line. They are arguing, as I understand it, that this change is so significant that all the clinical trials, all the clinical trials must be repeated to ensure that the change has not altered safety and effectiveness. Obviously, we are concerned about safety, but we also want to get the benefit and not have this argument about safety be used to deny us the benefit.

My question to you is: is it true that a change in a cell line will always necessitate repeating the original clinical trials?

Dr. WOODCOCK. No. We do not believe that. Again, any manufacturing change, whether the cell line, the DNA construct, the manufacturing process, the way the drug is purified, any of these could affect safety and effectiveness, and therefore data has to be submitted and a very careful look has to be taken to make sure that it hasn't. The amount of data that we would need or that anyone would need to make that evaluation depends, again, on the complexity of the product.

Mr. WELCH. All right. So the bottom line here is that you believe that you do not need, for safety, to repeat the entire clinical trial?

Dr. WOODCOCK. In some instances the manufacturer may not be able to show enough similarity and they may have to repeat much of the clinical program. In other instances they may be able to show an extreme amount of similarity, a very great similarity to prior product, and therefore would have very much smaller clinical trials needed, perhaps of immunogenicity.

Mr. WELCH. And that is an evaluation that you would feel confident, based on the information that you had at hand, that you could make?

Dr. WOODCOCK. Yes. FDA has a long history, as I said, of controlling the access to market after manufacturing changes for a very wide number of products for all pharmaceuticals on the market, and this is another example of that.

Mr. WELCH. I was going to ask another question, but you are starting to answer it. What scientific developments have allowed FDA to feel that confidence you are describing, that manufacturers of existing biologics can change cell lines, manufacturing facilities, and/or the fermentation processes without having it conduct those clinical trials?

Dr. WOODCOCK. Yes. And, as I said, sometimes they do and sometimes they don't. It really depends. The burden is on them, the manufacturer, to show through scientific data that the performance of the product after the change process is going to be the same as the performance of the product before the change.

Mr. WELCH. And are clinical trials always the most sensitive studies for detecting changes in safety or effectiveness due to process changes?

Dr. WOODCOCK. No. No, I think that is a common misconception. Clinical trials may be insensitive to certain types of changes, adverse effects, for example, that are rare or uncommon.

Mr. WELCH. Yes.

Dr. WOODCOCK. And we really need to use the scientific tool to assess the change in the product that is appropriate. It might be physical characterization or it might be a functional test. It might be evaluation of the purity of the product.

Mr. WELCH. Thank you. I yield the balance of my time.

Chairman WAXMAN. Thank you for yielding. You have another minute left on your time, so if the gentleman would permit I will take that minute if he will yield to me.

Dr. Woodcock, if FDA were given broad authority to require any studies necessary for approval of follow-on versions of PHS Act approved protein products, are you comfortable that the agency could use its discretion to ensure that only safe and effective products were made available to patients? I think you have answered that question several times, but let me just put it very clearly.

Dr. WOODCOCK. I think that FDA must do that. All right? We do not currently approve generic products unless they have absolutely met our standards and were follow-on products under 505(b)(2). We must maintain the confidence in our program and also our own scientific integrity.

Chairman WAXMAN. Based on your experience with the comparability guidance, can you give the committee a perspective on how often companies must do clinical outcome trials, not just PK or PD studies, to support a product or process change after ap-

proval of its BLA? Are large clinical outcome studies scientifically essential to support the approval 1 out of 10 post-approval product changes, 1 out of 20 post-approval changes, or 1 out of 50 changes?

Dr. WOODCOCK. I would say that the factor that is most important here is the magnitude of the change; however, it is probably more in the 1 in 50 range than the 1 in 10, or whatever. But don't forget there are many different types of changes that occur all the time to manufacturing processes. If you included all of those, then requiring clinical studies of outcomes would probably be quite rare.

Chairman WAXMAN. Thank you.

Mr. Bilbray.

Mr. BILBRAY. Mr. Chairman, I would like to yield my time to the gentleman from the Northwest Territory, but I would first like to clarify that, as a native Californian as opposed to Mr. Issa who is an immigrant, I was outraged at the concept of bringing a bottle of Merlot to this table and having it chilled. [Laughter.]

The only thing worse than that is to take it from the table and take it back to his office after he presented it.

But at this time I would like to yield to Mr. Burton.

Mr. BURTON. I thank the gentleman for yielding. I am from the Midwest, not the northwest.

Mr. BILBRAY. Well, the Northwest Territory.

Mr. BURTON. Ohio, the Northwest Territory. You are going back a long way.

First of all, let me preface my remarks by saying the pharmaceutical industry and FDA working together has created probably the highest quality of life in the history of mankind, and I appreciate that and I think everybody in America does. There are some questions, though, that I have to ask about the process.

You said it is a judgment call on whether or not this product comes to market. Who makes the judgment? Who makes the call?

Dr. WOODCOCK. The FDA.

Mr. BURTON. Don't they have advisory committees that review the process, review the product, review the results, and then they make a recommendation to the FDA?

Dr. WOODCOCK. Yes. Advisory committees are frequently utilized, particularly on clinical decisions. Here we are talking about scientific characterization of the product in a wide variety of ways. Most often, that is something that the FDA scientists do.

Mr. BURTON. But the FDA does have advisory committees for almost all of the products?

Dr. WOODCOCK. Yes.

Mr. BURTON. When I was chairman I asked—I don't believe it was you, but I asked one of your coworkers who was a leader at the FDA how many times has an advisory committee recommendation been turned down by the FDA.

Dr. WOODCOCK. You are asking me?

Mr. BURTON. Yes.

Dr. WOODCOCK. I don't know the answer to that.

Mr. BURTON. I will tell you what it was before. It was never. The advisory committee, I was told by the people who were doing the investigation for my committee when I was chairman, was that the advisory committee recommendations were always accepted.

Now, the other thing I would like to know is: the people on the advisory committee, do they file financial disclosure reports?

Dr. WOODCOCK. Yes, they do.

Mr. BURTON. We looked at some of the financial disclosure reports when I was holding hearings on this when I was chairman and we found that many of the people in the advisory committees did not file financial disclosure reports. And we found that some on the advisory committees had a conflict of interest. The RotoShield virus was one of those. The head of the advisory committee had an interest in a company that was going to make a RotoShield virus vaccine, which was put on the market at his advisory committee's recommendation, and FDA approved it based upon the recommendation. One or two children died and several people were injured and they pulled it off the market within 12 months.

I bring this up because this is a very important issue we are talking about today, and I would just like to ask that these advisory committees, when they make recommendation, that there is a thorough judgment made after the advisory committee makes its determination, and that the FDA does not always accept their results or their recommendations, and that there are complete financial disclosure reports.

The reason for that is pretty obvious. If a person is on an advisory committee and their recommendation is accepted and they have a financial interest in a pharmaceutical company that is going to manufacture a product like that or a like product, they are liable to have their judgment tainted just a little bit. It has happened in the past and I hope it doesn't happen in the future.

The cost of biotech drugs increased 17 percent from 2005 to 2006, and that was compared to 5.4 percent increase for traditional pharmaceuticals, which are much more expensive here than in some other countries, in most cases. Why was that increase so much? Do you know?

Dr. WOODCOCK. My understanding is that some of the new biotech products on the market that are very highly effective, you know, are very expensive to purchase, as some of the members already alluded to. But I don't have any complete analysis of this.

Mr. BURTON. I have a couple more questions, but I will wait.

Chairman WAXMAN. We will have another round.

Mr. BURTON. I will catch it next time.

Dr. WOODCOCK. May I?

Chairman WAXMAN. Yes.

Dr. WOODCOCK. The FDA has recently published new guidance on advisory committee conflicts of interest, and it lays out very explicit and transparent guidance on how people will be evaluated for their conflicts of interest.

Mr. BURTON. That is very good news. I appreciate hearing that. That is a great step in the right direction. Thank you.

Chairman WAXMAN. Thank you, Mr. Burton.

Mr. Davis.

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman.

Dr. Woodcock, I have always tried to understand—and if you could enlighten me it would be very helpful to me—the real difference between generic drugs and the brand name drugs. If they do essentially the same thing or if the level of effectiveness is es-

sentially the same, why do we pay so much more for one as opposed to the other? I have never been able to, in my own mind, feel that I had a real understanding of that.

Dr. WOODCOCK. Well, if I may, if you look at the diagram—it is gone now, but there was a diagram of the molecule up there, a small molecule. We know exactly everything how that molecule is structured. We know everything about it. And so what we do in the generic drug program is we require an exact copy of that molecule to be the generic drug and then we make sure that molecule gets into the body the exact same way that the innovator molecule gets into the body. So then we say if it does that it is going to have the same effect on the body because it is circulating around in the body the same way as the innovator drug. So that is what a generic drug is.

The problem with the proteins is it is very difficult to say we have the exact same molecule because it is such a complicated molecule.

Mr. DAVIS OF ILLINOIS. The effectiveness or the impact, are we saying that we would expect a different level of impact or effectiveness using one as opposed to the other?

Dr. WOODCOCK. For the generic drugs that FDA approves we expect the exact same performance. Now, that means the exact same good effects and the exact same side effects as the drug it is a copy of.

Mr. DAVIS OF ILLINOIS. Do you know then how the price or cost differential emerges or is determined?

Dr. WOODCOCK. Well, while the innovator drug is patent protected or protected by exclusivity, there are no other copies available to be prescribed. During that time the price is quite high. Once generic versions get in the market, the price of the various generic copies becomes only a fraction of what was charged by the innovator.

Mr. DAVIS OF ILLINOIS. Are you aware or familiar with any consumer studies that would indicate whether or not consumers have a greater level of confidence, for example, in the more popular pharmaceuticals than the generics?

Dr. WOODCOCK. Certainly the generics are not advertised and certainly there is some brand name loyalty that I have heard of. I have certainly talked to many, many consumers over my lifetime about this issue. There is some residual concern still about the generics and whether are they as good because they are not the brand name product; however, I think in the last 10 or 12 years of our generic drug program, confidence, both by the health professionals—the pharmacists, the doctors—as well as the consumers has really risen, and most people in this country are used to taking generic versions.

Mr. DAVIS OF ILLINOIS. And so then one could probably reasonably assume that marketing plays a great role in shaping our attitudes and thoughts about the drugs that we would most likely prefer using?

Dr. WOODCOCK. I can't comment on that directly, but that is one of the purposes of advertising.

Mr. DAVIS OF ILLINOIS. And so I would assume that it probably works fairly well and that it does, in fact, skew one's thinking. And

if we are talking about having the most cost-effective health care, then it just seems to me that the more enlightened consumers become, that will probably have as much impact on cost effectiveness in health care as anything that we are going to regulate or anything that we are going to do.

I thank you very much for your answers.

Dr. WOODCOCK. At the request of Congress, we had an education program, outreach program, on the generic drug program. It has been very effective.

Mr. DAVIS OF ILLINOIS. Thank you. Thank you very much.

And thank you, Mr. Chairman. I yield back.

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Burton was using Mr. Bilbray's time, and he said he had a few more questions, so before we go to a second round I yield to you your first-round 5 minutes.

Mr. BURTON. Thank you. I just have a few more questions.

Dr. Woodcock, I think you have been very helpful, some of your answers today. I really appreciate that.

The pharmaceutical industry deserves to get some of their money back or all of their money back when they spend a lot of money on research and development, and that is why the patents are there, and then when it expires, of course, it can be a generic drug and they should have recovered their investment.

Are other countries working to develop these biotech drugs?

Dr. WOODCOCK. Yes. As was alluded to earlier, the European Union has published a directive and is implementing a program on what they call biosimilars. By that generally they mean biotech drugs.

Mr. BURTON. If they produce a biotech drug and there is a similar biotech drug that has been produced here in the United States, because of the differences, the scientific differences that you were talking about when we saw the slide a while ago, the FDA probably would not allow that drug to be imported into the United States until it was approved by the FDA, even though it did the same thing or pretty much the same thing?

Dr. WOODCOCK. Yes. The law doesn't allow drugs to be imported in the United States unless they are approved.

Mr. BURTON. Let me ask you one more question. If we had reimportation or importation of the pharmaceuticals that are approved by the FDA, would the prices of those pharmaceuticals be lower?

Dr. WOODCOCK. Again, this is beyond my area of expertise. I apologize.

Mr. BURTON. I will just followup by saying that everybody wants free enterprise to succeed and they want the pharmaceutical industry to make a lot of money so that they can do continued research, but when my first wife had cancer—and I have talked about this before—we went to have her chemotherapy and the tamoxifen that one woman was taking, she was complaining about the cost being about $300 a month, and another lady said I'm getting the same thing from Canada for $50 a month, so it was six times less.

There are a number of us in Congress that would like to see the FDA working with their counterparts in other countries and the pharmaceutical companies working with their counterparts in other

countries and the governments of other countries to find out some way to level the playing field so that Americans are paying a comparable price for their pharmaceutical products as they do in other countries. It just doesn't seem fair to go to Germany or France or Spain or Canada and find that the very same product is being sold for much less, and Americans are paying actually a great deal more for the research and development and the advertising than is being paid elsewhere.

That is just a suggestion. I appreciate very much your candid answers.

I yield to the chairman.

Chairman WAXMAN. Thank you very much for yielding. The gentleman has a minute and a half, so I will be glad to take it.

If a statute were passed giving FDA broad authority to review abbreviated applications for follow-on proteins, and if companies were ready to begin submitting applications as soon as the statute became law, is it reasonable to assume that FDA would be able to begin reviewing those applications as soon as they were submitted, assuming, for the purpose of this question, that the statute did not require FDA to issue regulations or guidance as a prerequisite to the review of applications?

Dr. WOODCOCK. FDA is currently, as I said, reviewing applications and also inquiries from companies and so forth, providing guidance for drugs under the 505(b)(2) regimen. So we have the technical expertise to perform these functions.

Chairman WAXMAN. Thank you.

Mr. Hodes.

Mr. HODES. Thank you, Mr. Chairman.

Dr. Woodcock, I want to focus for a moment on the issue of comparability.

Dr. WOODCOCK. Yes.

Mr. HODES. It is my understanding that biologics as a group are so diverse and in some cases so incompletely understood that there is today no one-size-fits-all set of studies that can demonstrate comparability. Is that true?

Dr. WOODCOCK. Absolutely. Biologics, as opposed to biotech proteins, range from everything from gene therapy to cells, living cells of different types, to tissues—a huge range of different kind of products.

Mr. HODES. And am I correct that biopharmaceutical products often undergo changes after approval and that pre-change and post-change products will be comparable, as opposed to identical?

Dr. WOODCOCK. Yes. As we were discussing before, manufacturers need to continue to improve their process or they may need to open up new plants or increase the level of production, the scale of production. There are a lot of changes that have to be made. After each one of those changes, we must assess whether or not the performance of the product has changed.

Mr. HODES. And the FDA establishes boundaries and batches. Different batches have to fall within established boundaries for that product?

Dr. WOODCOCK. Yes. Any product, whether it is a small molecule or drug, has slight variations lot to lot in any kind of testing parameter that you would put on it, so the traditional approach is to

establish boundaries within which a product can vary, but it can't go outside of those limits.

Mr. HODES. Now, just as the science is evolving on the manufacturing side—certainly from the FDA's standpoint techniques for assessing the structure and activity of biologics are evolving rapidly—and our understanding of biological structure and activity is improving all the time; is that correct?

Dr. WOODCOCK. That is correct.

Mr. HODES. If Congress were to tell the FDA what specific types of clinical data must always be required for approval of follow-on biologics based on today's science, could such clinical data requirements become obsolete?

Dr. WOODCOCK. Certainly, from my point of view, flexibility in enabling us to incorporate the new science into the regulatory process as that science evolves and becomes available is in the best interest of the public as well as the agency and the industry.

Mr. HODES. And if a follow-on statute required a clinical trial in every case, could it end up requiring perhaps unnecessary and therefore potentially unethical trials in the future?

Dr. WOODCOCK. Where trials aren't needed, it is, you know, of questionable ethics to repeat them. So use of human subjects for trials that are not needed or done simply to check a box on a regulatory requirement are not desirable.

Mr. HODES. Let me ask you a question about the EU system. The EU regulations, as I understand them—imperfectly, I might add—require post-market surveillance; is that correct?

Dr. WOODCOCK. I can't speak exactly. The Europeans have the ability to require post-marketing surveillance for any approved pharmaceutical.

Mr. HODES. Does the FDA currently have any requirements for post-market surveillance?

Dr. WOODCOCK. We very frequently request post-marketing studies be performed at the time of approval, and those are agreed to by the firms.

Mr. HODES. So it is the manufacturers who are conducting the post-market surveillance?

Dr. WOODCOCK. Yes.

Mr. HODES. The FDA relies on the manufacturers for that post-market surveillance; the FDA doesn't do any of its own?

Dr. WOODCOCK. Right. The FDA conducts the adverse event reporting system, which is an adverse event reports from doctors and companies, and we do some limited studies, but in general we do not have the capacity to do post-marketing surveillance as you are describing.

Mr. HODES. Do you believe with biogenerics developing as rapidly as the field is developing, there should be expanded requirements for post-market surveillance?

Dr. WOODCOCK. All pharmaceuticals when they are approved for the first time have a fair amount of uncertainty still surrounding them about their performance, and particularly, as we have discussed already, any protein product that would be approved would continue to have questions about immunogenicity and perhaps other side effects that would probably need to continue to be looked at in the post-marketing period.

Mr. HODES. Can the FDA require post-marketing studies?

Dr. WOODCOCK. What we do is say to the company: you need to agree to conduct this study, and if you do then that is part of the approval the company agrees to do.

Mr. HODES. So, if I understand your answer, the answer is yes, the FDA does have the authority to require post-market studies?

Dr. WOODCOCK. At the time of approval.

Mr. HODES. And what proportion of post-market studies that you require are completed?

Dr. WOODCOCK. That is a complicated question. There are many different types of studies that are requested, and some of them go on a long time, so there isn't a really high proportion. I don't know the exact number, because it depends on what analysis you are doing, but many of these studies are not completed.

Mr. HODES. And if you were the last word on this, thinking about where the science is going with biogenerics, do you see a need for increased requirements for post-market studies of these biogenerics, none of which will ever be identical, either in batch or in actual structure, to the original?

Dr. WOODCOCK. I believe it would be likely in many cases, but, as I said, this is going to be case-by-case because of all the differences in the different products. In many cases FDA would need to have post-marketing surveillance or post-marketing studies done to resolve remaining uncertainties.

Mr. HODES. And, last question, does the FDA have an enforcement mechanism to require completion of any post-marketing studies that you have required of the manufacturers?

Dr. WOODCOCK. We can publicize the fact that the studies have not been done, and we could take the drug off the market.

Mr. HODES. So the enforcement mechanism is the possible removal of the drug from the market for lack of completion?

Dr. WOODCOCK. Yes.

Mr. HODES. Has that ever been done?

Dr. WOODCOCK. Not to my knowledge.

Mr. HODES. Thank you.

I yield back. Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you. That is called the guillotine, except it is never used.

Dr. Woodcock, I understand that it is quite a bit more complicated to establish interchangeability of two protein products than to establish their comparable safety and effectiveness. Would it be possible to demonstrate that a copy of a well-understood protein is interchangeable with the brand name drug if there are no limits on what studies can be required?

Dr. WOODCOCK. We believe so. The situation in health care right now is that products that are interchangeable, they may be repeatedly switched back and forth. All right? And where you have a situation where you have a number of similar products on the market, the same indication, and they are very similar, it might be that they can be switched back and forth among one another multiple times for a given patient, depending on the plan and who they contract with and so on. In that situation either the innovator product could cause antibodies to the follow-on product or vice versa. We

think we would have to test that in people to make sure, but we think it would be feasible to do those tests.

Chairman WAXMAN. Is our understanding of protein structure and activity likely to evolve in a way that will make it possible to establish interchangeability in the foreseeable future, at least for some of these proteins, that may not be obvious at the present time?

Dr. WOODCOCK. It may not be the protein, itself, that causes the immune response, but it could be different contaminants that are co-purified from the cell line or during the manufacturing process, or it can be changes that happen late in manufacturing or during storage or so forth, so it is really a very complicated situation.

Chairman WAXMAN. For very simple, well-understood proteins, what kinds of studies might be required to establish interchangeability?

Dr. WOODCOCK. Well, a study that actually performs that activity, which changes the patient back and forth from one version of the product to the next and follows the immune response.

Chairman WAXMAN. Would that be a difficult study?

Dr. WOODCOCK. No. In some cases there might be ethical issues that we would have to address very carefully. We would not want to set any patient up for harm.

Chairman WAXMAN. Might the study requirements lessen over time as the molecules are better understood?

Dr. WOODCOCK. Yes.

Chairman WAXMAN. Do you think that the FDA would ever declare a copy of a biotech drug regulated under Hatch-Waxman to be interchangeable if the agency had doubts about whether it could be safely substituted for the brand name product?

Dr. WOODCOCK. No. I mean, we believe that our finding of an A rating of interchangeability is our word. We are saying that scientifically we believe those products would be interchangeable, and we would not do that unless we believed that were the case and it was substantiated with scientific data.

Chairman WAXMAN. Do you think that the FDA could be trusted to make appropriate interchangeability determinations for protein products if the agency were given statutory authority to approve copies of biologics under the PHS Act?

Dr. WOODCOCK. I believe that the FDA can be trusted to carry out its mandate from Congress, whatever that might be.

Chairman WAXMAN. And if we gave you an additional mandate, you feel you would be able to live up to it?

Dr. WOODCOCK. Yes. I believe we have scientific expertise. As we have already discussed, we have been managing manufacturing changes for all pharmaceuticals on the market for a very long time.

Chairman WAXMAN. Thank you.

Let me see if any Member wishes additional time for questions?

[No response.]

Chairman WAXMAN. If not, let me thank you very much for your presentation and your willingness to answer these questions. I think it has been very helpful for us in our understanding of this issue. Thank you very much.

Dr. WOODCOCK. Thank you.

Chairman WAXMAN. The Chair would like to now call forward our second panel.

Dr. Geoffrey Allan is the president, CEO, and chairman of the Board of Insmed Incorporated located in Richmond, VA. Insmed is a biopharmaceutical company focused on the development and commercialization of drugs for the treatment of metabolic diseases and endocrine disorders with unmet medical needs.

Dr. Theresa L. Gerrard is now the president of TLG Consulting, Inc., where she assists pharmaceutical and biotechnology companies in product development and regulatory strategy. Prior to that she spent 11 years as a Division Director in FDA's Center for Biologics Evaluation and Research, and she has also previously served as director of development for Amgen.

Dr. Bill Schwieterman is a physician and scientist by training who now acts as an industry consultant to major biotech pharmaceutical companies on product clinical development issues. Dr. Schwieterman started his career at NIH and subsequently moved to FDA, where he worked for 10 years and served as the Chief of Immunology and Infectious Disease Branch within FDA's Center for Biologics Evaluation and Research.

Inger Mollerup has been the vice president for regulatory affairs at Nova Nordisk A/S since 2004. Nova Nordisk is a pharmaceutical company which focuses on diabetes care, as well as hemostasis management, growth hormone therapy, and hormone replacement therapy.

Dr. Ganesh Venkataraman is co-founder and senior vice president of research at Momenta Pharmaceuticals. Momenta Pharmaceuticals, Inc., is a biotechnology company located in Cambridge, MA focused on the treatment of disease through an understanding of sugars and complex biomolecules.

We are pleased to welcome all of you to our hearing today. We appreciate your being here.

It is the custom of this committee to put all witnesses under oath. You are not being singled out. I would like to ask you to please stand and raise your right hands.

[Witnesses sworn.]

Chairman WAXMAN. The record will reflect that each member answered in the affirmative.

We will make your prepared statements part of the record in its entirety. We would like to ask, if you would, to try to limit the oral presentation to around 5 minutes.

Why don't we start with Dr. Allan, and then we will move right down the line. You see we do have a timer. Dr. Allen.

STATEMENTS OF GEOFFREY ALLEN, PH.D, PRESIDENT, CHIEF EXECUTIVE OFFICER, CHAIRMAN OF THE BOARD, INSMED INC.; THERESA LEE GERRARD, PH.D, PRESIDENT, TLG CONSULTING, INC. (BIOPHARMACEUTICAL CONSULTANTS FORMERLY WITH AMGEN AND FDA'S CENTER FOR BIOLOGICS); BILL SCHWIETERMAN, M.D., PRESIDENT, TEKGENICS CORP. (BIOPHARMACEUTICAL CONSULTANTS FORMERLY WITH FDA'S CENTER FOR BIOLOGICS); INGER MOLLERUP, VICE PRESIDENT FOR REGULATORY AFFAIRS, NOVA NORDISK A/S; AND GANESH VENKATARAMAN, PH.D, SENIOR VICE PRESIDENT, RESEARCH, MOMENTA PHARMACEUTICALS, INC.

STATEMENT OF GEOFFREY ALLAN

Mr. ALLAN. Good morning, Chairman Waxman, Ranking Member Davis, and members of the Oversight and Government Reform Committee. I am delighted to have the opportunity to testify before your committee. The focus of my discussion will be the role of small, innovative biotechnology companies in the current debate regarding the development of a regulatory pathway for approving biogeneric drugs.

My name is Geoffrey Allan, and I currently serve as the chief executive officer of Insmed, Inc. Insmed is a small biotechnology company focused on the development and commercialization of drugs for the treatment of metabolic and endocrine disorders where there are clear unmet medical needs.

We received FDA approval for our lead product, IPLEX, at the end of 2005. IPLEX is a therapeutic protein which is approved for the treatment of children suffering from a rare growth disorder. We are currently continuing to develop IPLEX for several major medical illnesses such as myotonic muscular dystrophy and medical complications associated with HIV infection.

I am here today to talk about biogeneric drug development and the regulatory path forward. 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 and extent of clinical trials needed to support characterization of a generic biologic. Our experience tells us that these issues can be addressed using sound, readily available scientific approach.

Insmed has developed significant intellectual capital focused toward protein characterization and purification. We have invested in building a facility required to manufacture quality proteins. The biogenerics business is a business in which we would like to specialize. The combination of our proprietary protein platform with a biogeneric protein platform meets our goal to sustain innovation, along with the ability to provide safe and affordable drugs to address a growing economic issue.

It is my belief that there are a number of my colleagues in similar-sized companies that are also interested in providing the scientific expertise to meet the challenges of producing biogenerics. I believe that I am representing the interests of many smaller biotechnology companies and large contract manufacturing companies. I believe H.R. 1038 provides for a fair balance between reward and innovation in creating a timely approval pathway in commercializa-

tion of biogenerics in the marketplace; therefore, passing this bill would be a positive step for the biotech industry and continue to fuel the cycle of innovation.

As the chief executive officer of a small biotechnology company, I hope my testimony will provide a different perspective on this important issue and bring to light some of the important reasons why this bill is the correct model to create a robust, competitive, and innovation biopharmaceutical marketplace.

IPLEX is a recombinant protein product. In fact, it is a combination of two different recombinant protein molecules. It is a relatively large molecule, larger than insulin, growth hormone, the interferons, and Epogen, and certainly no less complex in its structural characteristics. As a new drug, along with the demonstration of safety and efficacy in the target population, structural characterization of the protein and the development of a quality manufacturing process was our central focus during the development of the product.

During the course of the development of this product, we modified the manufacturing process several times. We changed cell lines. We changed purification procedures. We changed raw material sources. And on more than one occasion we changed the facilities where this product was manufactured. At all times, good analytical methodology was the bedrock of our comparability testing to ensure that we produced a consistent, highly purified protein.

Analytical methodology to allow structural characterization of proteins has evolved enormously over the years. It is sophisticated and has exquisite sensitivity. For example, we use a battery of sensitive and analytical tests. More than 10 of these tests are used, one of which is a technology called mass spectroscopy. This technique has such high resolution that on certain molecules we can detect changes as small as a single proton within the molecule. This is essentially not a crude science.

During the development of IPLEX we worked closely with the FDA. They clearly used their discretion to decide what tests we needed to support our scientific approach as we made changes to our manufacturing processes. Their recommendations were rational and certainly not onerous. On the occasion that we changed the site of manufacture of the drug, moving our process from a U.K. facility to our own facility in Colorado, we conducted a simple pharmacokinetic study in human volunteers to establish the equivalence of the products after the facility change. We established very quickly, within 1 month, that the amount of drug in the bloodstream was consistent, regardless of where the drug was manufactured.

IPLEX was being developed for use in children, and as such both we and the FDA knew that safety at all times was paramount and was certainly never jeopardized. For example, FDA was concerned that immunogenicity of the product could vary as we changed the process. We established surveillance procedures to address this issue, and we continue to monitor for signs of immunogenicity today.

I have only given you a very brief overview of the type of scientific and technical issues we had to address in the development of this product, IPLEX; however, these issues are at the heart of

what a biogeneric manufacturer would have to confront. The science has reached a level of sophistication to make this endeavor entirely possible. All we need now is the regulatory go-ahead.

The proposal introduced by Chairman Waxman is extremely appealing as a next step in stimulating competition in order to address an ever-increasing economic problem facing our health care system. Based on our company's experience with the FDA during the approval process of IPLEX, I am confident that this legislation is based on sound science and progressive insight into where the market should be in the coming years.

Once again, thank you for this unique and important opportunity to share my experience and views. I look forward to your questions.

[The prepared statement of Mr. Allan follows:]

Statement of Geoffrey Allan, Ph.D.
President, Chief Executive Officer, Chairman of the Board
Insmed Incorporated

House Committee on Oversight and Government Reform
"Safe and Affordable Biotech Drugs – The Need for a Generic Pathway"
Monday, March 26, 2007

Good morning Chairman Waxman, Ranking Member Davis and Members of the Oversight and Government Reform Committee. I am delighted to have the opportunity to testify before your Committee. The focus of my discussion will be the role of small innovator biotechnology companies in the current debate regarding the development of a regulatory pathway for approving biogeneric drugs.

I currently serve as the Chief Executive Officer of Insmed Incorporated. Insmed is a small biotechnology company focused on the development and commercialization of drugs for the treatment of metabolic and endocrine disorders where there are clear unmet medical needs. We received FDA approval for our lead product IPLEX at the end of 2005. IPLEX is a biologic, which is approved for the treatment of children suffering from a rare growth disorder. We are continuing to develop IPLEX for several major medical illnesses such as myotonic muscular dystrophy and medical complications associated with HIV infection.

I am here today to talk about biogeneric drug development and the regulatory path forward. 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 and extent of clinical trials needed to support characterization of a generic biologic. Our experience tells us that these issues can be addressed using a sound, readily available scientific approach.

Insmed has developed significant intellectual capital focused towards protein characterization and purification. We have invested in building the facilities required to manufacture quality proteins. The biogenerics business is a business in which we would like to specialize. The combination of our proprietary protein platform with a biogeneric protein platform meets our goal to sustain innovation along with the ability to provide safe and affordable drugs to address a growing economic issue.

It is my belief that there are a number of my colleagues in similar size companies that are also interested in providing the scientific expertise to meet the challenges of producing biogenerics. I believe that I am representing the interests of many smaller biotechnology companies and large contract manufacturing companies. I believe H.R.1038 provides for a fair balance between rewarding innovation and creating a timely approval pathway and

commercialization of biogenerics in the marketplace. Passing H.R.1038 would be a positive step for the biotech industry and continue to fuel the cycle of innovation.

As Chief Executive Officer of a small biotechnology company I hope my testimony will provide a different perspective on this important issue and bring to light some of the important reasons H.R.1038 is the correct model to create a robust, competitive and innovative biopharmaceutical marketplace.

IPLEX is a recombinant protein product, in fact it is a combination of two different recombinant protein molecules. It is a relatively large molecule, larger than insulin, growth hormone, the interferons and epogen and certainly no less complex in its structural characteristics. As a new drug, along with the demonstration of safety and efficacy in the target population, structural characterization of the protein and the development of quality manufacturing processes was our central focus during the development of the product. During the course of development we modified the manufacturing process several times. We changed cell lines, purification procedures, raw material sources and, on more than one occasion the facilities. At all times, good analytical methodology was the bedrock of our comparability testing to ensure that we produced a consistent, highly purified protein. Analytical methodology to allow structural characterization of proteins has evolved enormously over the years. It is sophisticated and has exquisite sensitivity. For example, we use a battery of sensitive analytical tests, more than 10, one of which is a technique called mass spectroscopy which has such high resolution that we can detect changes as small as a single proton within the molecule. This is not a crude science.

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I have only given you a very brief overview of the type of scientific and technical issues we had to address in the development of IPLEX. However, these issues are at the heart of what a biogeneric manufacturer would confront. The science has reached a level of sophistication to make this endeavour entirely possible, all we need now is the regulatory go ahead.

The proposal introduced by Chairman Waxman is extremely appealing as a next step in stimulating competition in order to address an ever growing economic problem facing our healthcare system. Based on our company's experience with the FDA during the approval process of IPLEX, I am confident that the Waxman legislation is based on sound science and progressive insight into where the market should be in the coming years. Thank you again for this unique and important opportunity to share my experience and views. I look forward to your questions.

Chairman WAXMAN. Thank you very much, Dr. Allan.

Dr. Gerrard.

STATEMENT OF THERESA GERRARD

Ms. GERRARD. Good morning, Chairman Waxman, Ranking Member Davis, and members of the committee. My name is Theresa Gerrard. Thank you for allowing me the opportunity to testify this morning on the importance of establishing a science-based, abbreviated approval pathway for biogenerics.

From 1984 to 1995 I was with the FDA and was a Division Director with responsibility for IND and BLA review of hundreds of biotech products. I chaired licensing committees for Amgen's Neupogen, Genentech's Actimmune, and was involved in the review of beta Interferon from Chiron and Biogen.

After leaving FDA, I was director of development for Amgen in Boulder, CO, where I had oversight of development of several biotech products. For the past 9 years I have worked as a consultant, where I have worked with many companies, primarily brand biotech companies.

The purity of biotech products and the sophistication of analytical testing that exists today allowed the production of safe biotech drugs. Analytical testing consists of multiple sophisticated tests that are used to assess the physical, chemical, and biological characteristics of the product. Many more tests are used to assess a biologic than are typically used to assess a drug, because biotech products are more complex than drugs.

These tests set the product specifications or goalposts, if you will, for every batch of biotech product that must fall between these goalposts. This is because no two batches of biotech products are identical. There are always minor variations.

The advances in analytical characterization for well-characterized biologics allowed FDA to develop scientific policy officers on comparability in the early 1990's. This gave brand manufacturers the ability to change the manufacturing processes without the need for redoing the original clinical outcome trials if the product generated by the new process was shown to be comparable to product made by the old process.

Now, when we speak of biologic, the focus is on comparability. Why? Because no two batches of biologic product, whether brand name or generic, will ever be identical. Therefore, biologics are and should always be discussed in the context of comparability. Yes, small changes in manufacturing could have an impact on the final product, but we have known this for more than a decade and can detect these changes.

For the past 15 years, FDA has gained substantial experience and expertise in assessing manufacturing changes and comparability data for a large number of protein products. The underlying scientific principles that guided comparability policy are still valid and can and should be adopted for generic biopharmaceuticals. Why? Because the types of post-approval brand product changes are reflective of the issues biotech and generic companies will face in bringing generic biotech products to the market.

The primary premise of comparability is that analytical testing is the most sensitive method to detect differences between two

products. Clinical trials are rather insensitive in detecting product differences because the variation among people and their responses to a biopharmaceutical do not allow one to detect subtle product differences. Analytical testing, by itself, will not be sufficient in every case to demonstrate that a generic will have the same safety and efficacy as the brand name biotech product. In those cases, FDA can require additional data such as animal studies, human pharmacokinetic studies, or even clinical trials. There is not a one-size-fits-all model, but FDA can determine the amount of data needed based on the complexity of the product, the history of the clinical use, and the extent of analytical characterization to determine its comparability with the brand name product.

Before concluding, the question of immunogenicity has been raised in the discussion of both brand name and generic biopharmaceuticals, and I would like to take a moment to just briefly touch on this topic.

Immunogenicity means the body generates antibodies to a specific foreign substance, such as bacteria, and it is a normal response in keeping people healthy. People routinely make antibodies to many different substances and experience no negative effects. Some biologics can cause people to generate antibodies which are specific to that product, but most will not have any affect on safety or efficacy. For some to imply that immunogenicity reactions are always harmful is just plain incorrect.

FDA can assess the risk for immunogenicity when it reviews the products for purity, safety, and overall quality and can request additional clinical data when necessary. While immunogenicity is an important consideration for biogenerics, it is certainly not a hurdle to their development.

Mr. Chairman, the science exists for a creation of a clear, efficient, abbreviated biogeneric approval pathway. Analytical tests, combined with additional data when needed, would ensure the safety and efficacy of generic biopharmaceuticals.

Thank you.

[The prepared statement of Ms. Gerrard follows:]

Statement of Theresa L. Gerrard
TLG Consulting Inc.
Committee on Oversight and Government Reform
Safe and Affordable Biotech Drugs — The Need for a Generic Pathway

March 26, 2007

Good morning Chairman Waxman, Ranking Member Davis and Members of the Committee. My name is Theresa Gerrard. Thank you for allowing me the opportunity to testify this morning on the importance of establishing a science-based abbreviated approval pathway for biogenerics. As a scientist and a former FDA official, I believe that an abbreviated approval pathway can bring to patients affordable biogenerics that are, above all, safe and effective.

By way of introduction, I graduated from Cornell University where I majored in Biochemistry and I received my Ph.D. in Immunology from Virginia Commonwealth University's Medical College of Virginia. My postdoctoral training was at the National Institute of Allergy and Infectious Diseases, NIH where I trained under Dr. Tony Fauci. My research was focused on understanding human immune response to antigens. From 1984 to 1995, I was with the FDA in various positions from Staff Fellow to Division Director for the Division of Cytokine Biology. This Division is now called the Division of Protein Therapeutics. I was the Chairman of the licensing committee for Amgen's Neupogen, Genentech's Interferon-gamma and oversaw the licensing of Chiron's Betaseron and Biogen's Avonex. As the Division Director, I was responsible for the regulatory and research activities of the Division, which included review of INDs, BLAs and postmarketing actions for cytokine products such as interferons and growth factors. While at the FDA, I was involved in developing policies on the comparability of well-characterized products. It is fair to say that I reviewed hundreds of biotech products during my tenure at the Agency.

After leaving FDA, I was Director of Development for Amgen in Boulder, CO where I had oversight of clinical and product development for several recombinant protein products. We developed clinical programs, regulatory strategies and resolved product and manufacturing issues for biotechnoloy products for rheumatoid arthritis, hepatitis C, and oncology. I also served as the clinical team leader for consensus interferon (Infergen). This included filing an FDA license application, analyses of ongoing studies, and planning for postmarketing studies.

Since 1998, I have been an independent consultant to biotechnology and pharmaceutical companies. I have worked with many companies, primarily brand or innovator companies, in the areas of regulatory strategy and product development. I have worked with many companies in reviewing manufacturing changes during development and after FDA approval and have evaluated the manufacturing changes as part of the overall clinical development program. I have worked on many chemistry and manufacturing issues for protein therapeutic products and have also been involved in the

clinical development for many products. During the past 10 years, I have authored a number of papers and presented lectures on manufacturing changes, comparability and immunogenicity.

My testimony today will focus first on the role of analytical testing in the characterization of biopharmaceuticals and the determination of comparability to ensure safety and efficacy. I will also address the issue of immunogenicity.

THE SCIENTIFIC ADVANCEMENT OF ANALYTICAL TESTING

Every biological product is subjected to rigorous analytical testing. The same would hold true for biogenerics. Analytical testing consists of multiple tests that are used to assess the physical, chemical and biological characteristics of the product. Many more tests are used to assess a biologic than are typically used to assess a drug. This battery of tests is conducted for every batch of biopharmaceutical product manufactured and is also used to monitor the product during the manufacturing process. In the field of biopharmaceuticals both the Food and Drug Administration (FDA) and industry rely on analytical testing to ensure consistency so that every batch of the biopharmaceutical will be deemed safe and effective for its intended use.

Many biologics, including almost all of the biotech products, can be now defined by chemical and physical attributes. This fact can be attributed to two scientific advances. The first is the increasing purity of biological products, especially recombinant biotech products. The production of human proteins through recombinant technology continuously improves, providing ever more highly purified human proteins. The second advance is the increasing sophistication of the analytical technology that allows a very detailed characterization of these products. Although the cells that are used to produce biopharmaceuticals are complex living organisms, all finished biopharmaceutical products used to treat patients are highly purified human proteins that are produced consistently using advanced manufacturing technologies. The large array of sophisticated analytical tools that exist today now allow for the characterization of biopharmaceuticals to ensure safety and efficacy.

The advances in analytical characterization and the ability to assess the specified or well-characterized biologicals by analytical tests allowed FDA to develop scientific policies on comparability in the early 1990s. These policies gave brand manufacturers the ability to change the manufacturing process without the need for clinical trials if the new product was shown to be comparable to the previous product. Prior to this time, every change in a manufacturing process necessitated the need for new clinical data. It was the innovator biotech manufacturers who pressed FDA for this change, because they rightly claimed that their biopharmaceuticals were so well characterized. They proved this through their ability to identify potential product changes with analytical testing technology.

The brand companies fought for these policies because the need to make manufacturing changes for biotech products was common and manufacturers wanted to

make changes to the manufacturing process without the need to repeat clinical trials. FDA agreed that the nature of the products allowed manufacturing changes to be assessed predominantly by analytical testing for characterization. In fact, and this is a critically important point, FDA recognized that analytical testing was far more sensitive in the ability to detect product changes than a typical clinical trial. For the past 15 years, manufacturers of well-characterized biopharmaceuticals have been able to make manufacturing changes without repeating clinical trials if they demonstrate that the product made after the manufacturing change is comparable to the product made before the change.

Prior to 1996, FDA placed as much emphasis on licensing the manufacturing site as it did on characterizing the final product. In particular, CBER required both a Product License Agreement (PLA) and an Establishment License Agreement (ELA) for product approval. The ELA was specific to the facility and process used for that product. When FDA stopped requiring ELAs, it acknowledged a significant shift in the agency's understanding regarding the assessment of biopharmaceuticals. This change in policy signaled FDA's growing confidence in its ability to determine comparability, and thus, safety and efficacy, based on results from analytical testing of the finished product, independent of the manufacturing process. FDA also recognized that changes to the manufacturing process were common in the industry and that in most cases analytical testing could support these changes without need for retesting the product in clinical trials.

COMPARABILITY

When we speak of biologics, the focus is on comparability—no two batches of a biologic product, whether brand or generic, will be identical. Therefore biologics should always be discussed in the context of comparability. What does demonstration that two products are comparable mean? Successful demonstration of comparability between two biopharmaceuticals produced by different manufacturing processes does not necessarily mean the two products are identical in every way. Minor differences in the products manufactured by two different processes will be noted, however the products will be comparable. Likewise, biopharmaceutical products often undergo changes after approval and the pre-change and post-change products will be comparable, not identical. The fact is that every batch of a brand biopharmaceutical is simply not identical to the previous batch, but FDA establishes boundaries and all batches must fall within the established boundaries for that product.

Answering the question, "what is comparable" is determined on a case-by-case basis using multiple analytical tests to characterize the physical and chemical attributes of biopharmaceuticals. These analytical tools allow manufacturers to determine essential characteristics such as the sequence of amino acids, secondary and tertiary structures, and purity, among other physical and chemical features. For simple proteins, such as interferons, defining and demonstrating comparability is fairly simple. Alpha interferons are small proteins without glycosylation so analytical testing of the amino acid sequence, purity, bioactivity and aggregation is relatively straightforward. On the other hand,

complex proteins, such as antibodies, would need additional testing (e.g., carbohydrate analyses and glycoform heterogeneity) because these are larger and are glycosylated (have sugar molecules on the protein).

It bears mention that analytical testing is only one method for establishing the comparability of biological molecules. The amount of data needed to demonstrate comparability may depend on the complexity of the product and the significance of the manufacturing change. Analytical testing is regarded as the most precise measure of a molecule's attributes and thus serves as the first tier for comparability determination. If product differences are observed in analytical testing, then additional preclinical or pharmacokinetic tests may be warranted. Other methods include human pharmacokinetic and pharmacodynamic testing, and even clinical trials. This is dealt with on a case-by-case basis within the FDA. Often a tiered approach is used to assess products. If differences are observed after additional testing, or if there is insufficient product knowledge of the impact of differences, FDA has the discretion to ask for data from clinical studies or decide that products are not comparable and, therefore, not approvable.

As stated earlier, it is common for brand biopharmaceutical companies to implement manufacturing changes. It would be impracticable or impossible to make manufacturing changes if it resulted in undetectable changes that affect the product's safety or efficacy. In other words, if the complexity of biopharmaceuticals were as daunting as some maintain, then the current explosion of new biopharmaceuticals would be impossible. Manufacturers faced with unknowable or insurmountable complexities would simply not be able to assure consistency in the production of multiple lots of their biopharmaceutical or to assure comparability after changes to the manufacturing process.

During the past 15 years, FDA scientists have gained substantial experience and expertise in assessing manufacturing changes and comparability data for a large number of proteins. These range in complexity from the simple, low molecular weight, non-glycosylated proteins, such as insulin to complex, high molecular weight, glycosylated proteins, including monoclonal antibodies. The FDA allows the use of analytical testing to establish product comparability even following major manufacturing changes. For instance, in the case of Biogen's Avonex and InsMed's Iplex, the manufacturers changed the cell line, and the purification scheme and additionally for Avonex, the manufacturing site. In both cases, pre- and post-change product comparability was demonstrated to FDA's satisfaction without need for clinical trials to approve the post-change product.

Both Avonex and Iplex are complex products. The well-established methods for making comparability assessments allow biopharmaceutical manufacturers to change manufacturing sites, host cells, purification processes, and other aspects of production while ensuring that the products remain comparable from year-to-year and batch-to-batch. In another example, data presented on several manufacturing changes for Enbrel, a complex glycoprotein used to treat arthritis, noted that such changes were implemented after demonstration of comparability that included analytical and pharmacokinetic data.

FDA's policy on comparability has been very successful in ensuring safety and efficacy and has allowed brand manufacturers to implement manufacturing changes to bring products to market sooner. The underlying scientific principles that guided comparability policy are still valid and could be adopted for generic biopharmaceuticals. The primary premise is that analytical testing is the most sensitive method to detect differences between two products. Clinical trials are rather insensitive in detecting product differences because the variation among people in their response to a biopharmaceutical does not allow one to detect subtle product differences. However, FDA has the discretion to require any data that is needed to assure the safety and efficacy of the generic biopharmaceutical including clinical trials.

Undoubtedly, comparability will involve studies of the primary structure of the protein (that the requisite amino acids are present in the proper sequence), studies of potential changes to those amino acids (such as oxidation or deamidation), and that the protein has the proper three-dimensional structure ("folded" correctly). Comparability will also involve studies to show that the innovator and biogeneric proteins have a comparable level of purity. Comparability may also include testing to show that the innovator and biogeneric proteins have similar behaviors in biological assays. Again, FDA has established rigorous standards to assure that all biopharmaceuticals, irrespective of manufacturing processes, are safe and provide expected efficacy benefits to patients.

While state-of-the-art analytical technologies are the cornerstone for establishing comparability, such determinations may also be based on a variety of other testing methods. As I mentioned, pharmacokinetic, pharmacodynamic and/or confirmatory abbreviated clinical studies are currently used to address the specific concerns related to certain products.

The available spectrum of comparative tests would allow comprehensive evaluation of brand and biogenerics. With FDA's extensive experience in evaluating comparability data, it is possible to extend the concept of demonstrating comparability through non-clinical studies to the approval of biogeneric. Just as it currently does when brand companies make changes and comparability cannot be determined, FDA could require more data, including clinical studies, or not approve a biogeneric if it determined that comparability was not established through analytical testing to determine safety.

IMMUNOGENICITY

The question of immunogenicity has been raised in the discussion of both brand biopharmaceuticals and biogenerics. Therefore, I thought it was important to provide a scientific assessment of immunogenicity. Immunogenicity is the ability of a substance to stimulate the body's immune response, which usually means the generation of antibodies that are specific to the substance. The generation of antibodies to foreign substances, such as bacteria, is a normal response in keeping people healthy. People routinely make antibodies to many different substances and experience no negative effects. Sometimes a biopharmaceutical can cause people to generate antibodies, which are specific to that

biopharmaceutical. This sometimes occurs even though the biopharmaceutical is a highly purified human protein and is the same as the natural human protein.

In most cases, the antibodies to biopharmaceuticals are only temporary and have no adverse consequence. Even with antibody formation, most patients can continue to be treated effectively with the biopharmaceutical and there will be no difference in the side effects. The development of immunogenicity is never a reason to discontinue treatment with a biopharmaceutical unless there is reason to believe that the antibodies have rendered the biopharmaceutical or its natural counterpart ineffective. This situation is very rare.

Most impurities found in biopharmaceuticals today exist in minute amounts and do not cause immunogenicity. One factor that commonly has been associated with the immunogenicity of biopharmaceuticals is aggregation. Aggregation occurs when proteins interact to form large clusters of molecules. Aggregation can and should be monitored in the analytical testing of every lot of biopharmaceuticals and as part of the stability program over the shelf-life of the product. Many brand biopharmaceutical products were approved in an era when the importance of testing for aggregates was not recognized and, therefore, there is often no assessment of aggregates. Frequently, the analytical test procedures for the brand biopharmaceutical have not changed in many years and sometimes have not changed since the original FDA approval. Today, there are several methods available to test for the presence and size of aggregates. Biopharmaceuticals that would be approved by the FDA today, including biogenerics, would include this important testing for aggregation as a way to minimize any potential risk of immunogenicity.

There is no reason to believe that a biogeneric would have greater immunogenicity than the brand biopharmaceutical. Even if a generic manufacturer uses a different method to produce the biopharmaceutical, every lot of the biogeneric would be carefully analyzed and tested to assure that the product is safe and that any impurities such as aggregates, that might be associated with immunogenicity, are removed. FDA carefully reviews the manufacturing process for generic drugs; how these drugs are tested; and the results of the analytical tests. FDA would do the same for biogenerics as well. As stated earlier in my testimony, FDA has significant experience in the review of many types of biopharmaceutical products and the analytical methods to characterize these products. Moreover, with a biogeneric, the FDA has the benefit of many years of marketing history and a record of the safety and immunogenicity of the brand biopharmaceutical. Since the biogeneric would be analytically comparable to the brand product then immunogenicity would be expected to be similar.

FDA has more than two decades of experience with evaluating brand biopharmaceuticals for immunogenicity. Therefore, FDA can assess the risk when it reviews the products for purity, safety and overall quality. When the need arises, FDA can request additional testing including clinical testing to assess immunogenicity. While immunogenicity is an important consideration for biogenerics, it is certainly not a hurdle to their development. For those limited situations when additional supporting data is

required, clinical testing can augment comparability and aggregation studies. Finally, generic biopharmaceuticals will be subject to the same post-approval surveillance requirements as brand products that monitors patient safety.

SUMMARY

The science exists for the creation of a clear, efficient abbreviated approval pathway for biogenerics to ensure safety and efficacy. FDA currently reviews the data from sophisticated and advanced scientific analytical tools to assess the impact of changes made by the brand industry to their biopharmaceutical products. These analytical tests have been deemed to be the most sensitive technologies to ensure safety and efficacy of products that are changed by the brands. Moreover, this well-established approach to testing, used routinely by the brand industry, has significantly reduced the need for clinical studies and has resulted in bringing safe and effective life saving biopharmaceuticals to consumers.

Using the same scientific principles that were the basis for this current effective process for testing comparability, it is scientifically sound and practical to approve biogenerics based on a clear and efficient abbreviated approval pathway that will ensure safety and efficacy.

Chairman WAXMAN. Thank you very much, Dr. Gerrard.

Dr. Schwieterman.

STATEMENT OF WILLIAM SCHWIETERMAN

Dr. SCHWIETERMAN. Good morning, Chairman Waxman and members of the Committee on Oversight and Government Reform.

My name is Dr. William Schwieterman. I thank you for the opportunity to appear before the committee today and present the 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. For this reason, I deeply share your goal, Congressman Waxman, of creating a sound, scientifically based 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 your goal can and should be achieved.

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 to the committee.

First, with today's scientific advancements and technologies, we can assure the safety and efficacy of biogenerics.

Second, the supporting science for this is not new. It has existed for over a decade.

Third, the issues raised in post-approval brand changes are reflective of the issues that are raised in the field of biogenerics. As such, the same science that determines comparability for the brand tech industry can also be adopted to ensure the safety and efficacy of complaint and interchangeable biogenerics.

Having worked extensively with agency physicians and scientists, it is clear to me that 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 name or a generic.

The standards and science used for current biopharmaceuticals are informative to us with respect to biogenerics. A critical but not often publicized fact in the biopharmaceutical industry is that FDA does not require brand name 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 analytical comparability data. With these data, and keeping in mind the nature of the drug, the tests used, and the disease being studied, FDA decides how to proceed. The agency can give a thumbs-up or a thumbs-down regarding each post-approval brand manufacture change and, if thumbs-up, have that change be supported by the analytic data, alone. The analytic data, coupled with pharmacokinetic and/or pharmacodynamic studies or the analytic data—the studies just mentioned—plus data from a large clinical outcome study.

As you already have heard, the vast majority of brand name manufacturing changes need no further studies when data from analytic tests show the products to be comparable. For a small number of brand name products that show small differences in these analytic tests following manufacturing changes, FDA may require additional analytic tests and pharmacokinetic or pharmacodynamic tests to be conducted in animals or humans.

These later studies, PKBPD studies, are clinical studies in the sense that they are conducted in patients in the clinic, but they are not the large clinical 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 in general last weeks, not many months.

Rarely after a brand name manufacturing change does the FDA require that a brand name company take the last step, repeating a full-scale clinical outcome study. Such studies are not usually necessary because the variability and "noise" involved in most clinical outcome studies make them inefficient for determining comparability between agents. In fact, of all the hundreds of brand name biologic product changes, the vast majority were approved without large clinical outcome trials.

In sum, FDA's scientists and physicians routinely make comparability determinations, since manufacturing changes occur throughout the brand name biologic product development and life cycle. The comparability algorithm has existed for over a decade to allow brand name biologic manufacturers to change and improve their manufacturing processes.

In closing, I want to emphasize to the committee again that the science of comparability is not a new one, but rather an old one used by the agency and the brand name industry for more than a decade to determine comparability.

Chairman Waxman, the Access to Life-Saving Medicines Act will give FDA the authority and the flexibility it needs to ensure the safety and efficacy of biogenerics. I commend you for adopting the same scientific principles, processes, and procedures that exist for the brand name biologic industry when making post-approval manufacturing product changes to the biogeneric sector.

My mission as a physician reviewer at FDA, and that of all my colleagues, then and now, is to protect the public by ensuring the safety of the supply of biopharmaceuticals. No one's interests is served if safety is not viewed as paramount.

Thank you very much.

[The prepared statement of Dr. Schwieterman follows:]

William Schwieterman, M.D.
Testimony before the Committee on
Oversight and Government Reform
Safe and Affordable Biotech Drugs -- The Need for a Generic Pathway
March 26, 2007

Good morning Chairman Waxman and members of the Committee on Oversight and Government Reform.

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 Waxman and the other distinguished members of this Committee for the opportunity to testify on this important public health issue.

Congressman Waxman, for over twenty years you have been a leader in Congress on efforts to ensure greater public access to affordable medicines. It is fitting that you have taken the initiative to expand access to today's biopharmaceutical medicines. And as a physician, I know only too well that we as a society need to continue to foster medicial 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 your goal, Congressman Waxman, of creating a sound, scientific – based 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.

- 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.

My former colleagues and I had many responsibilities at the FDA, but our 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 post-approval 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.

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.

Let's assume for sake of this discussion that, the 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 post-approval 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.

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. 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 current bill proposes implementation of much of the same scientific processes and procedures that exist for the brand biologic industry when post-approval 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.

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. The analytic tools presently used in the

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[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.

brand biotech industry to ensure comparability can also be used to ensure the safety of biogeneric agents. Product characterization, use of pharmacokinetic and/or pharmacodynamic studies and, if necessary under certain circumstances, data from clinical outcome studies can and have been used for this purpose.

We can and should draw upon existing science to help bring affordable biopharmaceuticals to the marketplace.

I have had the privilege of working in this area and seeing firsthand how biotechnology is transforming the lives of certain Americans treated with these agents. The current bill allows for the promise of biotechnology to reach far and wide in this country, for the benefit of all.

Chairman WAXMAN. Thank you very much, Dr. Schwieterman.

Ms. Mollerup.

STATEMENT OF INGER MOLLERUP

Ms. MOLLERUP. Chairman Waxman, Ranking Member Davis, members of the committee, thank you for inviting me to testify today. My name is Inger Mollerup. I am vice president for regulatory affairs of Nova Nordisk, a company with an 80-year history of producing insulin and other proteins.

I am a scientist, not a lawyer, and as such have for the last 30 years been engaged in the design of manufacturing processes and development programs for numerous recombinant proteins. In 2005 I represented the drug before the European Medicines Agency [EMEA], discussing the insulin follow-on guidance, and I also presented to the World Health Organization's INN Committee on issues related to naming of all therapeutic proteins, including follow-ons.

Nova Nordisk believes that any pathway for follow-on biologics must be, first and foremost, constructed to protect patient safety, be rooted in the best science, preserve innovation, and respect proprietary information.

Three major points from my testimony today are: first, that characterization does not tell the whole story; second, that pre-clinical and laboratory tests are not sufficient to determine immunogenicity and other important safety parameters; and, third, that current science does not support interchangeability.

First, characterization does not tell the whole story. Any pathway must fully address the patient safety considerations of medicines that are similar to or comparable to instead of the same as the reference product. Given that proposals currently before Congress go far beyond the science in an effort to deem products having minor differences in immuno-acid sequence as highly similar, I share with you an experience we had at Nova Nordisk as we were developing a fast-acting insulin analog wherein two potential candidates with one amino acid difference were tested.

All candidates were put into an extensive chemical preclinical and clinical program. The candidate taken to market had only one change to the immuno acid sequence from human insulin, resulting in an analog with significantly shorter timing of action than human insulin and a unique safety profile.

An earlier candidate, which had also one amino acid substitution, showed a positive effect on the timing of action, but in full preclinical animal toxicology studies this dark candidate significantly elevated tumor potential in rats. Development of this candidate was immediately discontinued.

Even though both analogs were fully characterized, an animal study was required to demonstrate that this seemingly minor difference had enormous consequences for important safety characteristics. Minor differences can have major safety consequences.

Second, pre-clinical and laboratory tests are not sufficient to determine immunogenicity and other important safety parameters. Human clinical immunogenicity data must be required, and we have numerous examples illustrating its vital importance.

While developing a complete new process for our insulin analog, we discussed this program with the FDA. FDA stated the no general safety threshold could be applied for new impurities. Even one as low as 0.1 percent was not acceptable because proteins can be immunogenic at very low concentrations, and it is not known when low is low enough. Immunogenicity data from an appropriate clinical study was, therefore, necessary and included in our submission.

Third, current science does not support interchangeability. Based on today's science, a follow-on biologic cannot be determined to be the same as a innovator drug. For this reason and because of the potential difference in immunogenicity and other drug-specific adverse events, follow-on biologic products must not be allowed to be interchangeable. The treating physician must at all times be involved in the decision to change from one product to another.

Interchangeability is also not part of the EMEA approval, and Europe has the further requirement that these products are clearly identified to support post-market monitoring.

Nova Nordisk believes that any pathway for follow-on biologics must be, first and foremost, constructed to protect patient safety, be rooted in the best science, preserve innovation, and respect proprietary information.

Thank you for the opportunity to speak here today. Nova Nordisk is ready to assist Congress as this issue moves forward.

[The prepared statement of Ms. Mollerup follows:]

Statement of Inger Mollerup, MSc

Vice President

Novo Nordisk A/S

Before the

Government Oversight and Reform Committee

Hearing On

"Safe and Affordable Biotech Drugs – The Need for a Generic Pathway"

March 26, 2007

Statement of Inger Mollerup, MSc
Vice President, Novo Nordisk A/S
Government Oversight and Reform Committee
March 26, 2007

Chairman Waxman, Ranking Member Davis, and members of the Committee, thank you for inviting me to testify today. My name is Inger Mollerup and I am Vice President for Regulatory Affairs at Novo Nordisk A/S. Novo Nordisk is a healthcare company with an 80-year history of innovation and achievement in diabetes care. In addition to diabetes care, Novo Nordisk has a leading position within areas such as hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk's business is driven by the Triple Bottom Line: a commitment to economic success, environmental soundness, and social responsibility to employees and customers. Our global headquarters are in Denmark and our U.S. headquarters are in Princeton, New Jersey.

For approximately 30 years, I have been involved in the design of manufacturing processes and development programs for a number of recombinant proteins for Novo Nordisk. With this background, in December 2005, I presented before the European Medicines Agency (EMEA) as part of a panel on guidelines for biosimilar insulins (biosimilars is the term for follow-on biologics in Europe) and then

presented before the World Health Organization INN Committee in November 2006 on the topic of naming biosimilars. Novo Nordisk wants to work closely with Congress as it considers the best way to establish a legal and regulatory pathway for biosimilars, or follow-on biologics as they are called in the United States.

The creation of an entirely new approval pathway for a new class of drug products not presently on the market is an enormous undertaking with serious consequences for literally millions of patients. Novo Nordisk believes any pathway for follow-on biologics should be rooted in the best science, preserve innovation, respect proprietary information, and most importantly be constructed to protect patient safety. Based on my experience with all of the therapeutic proteins I have worked with over the years, it is clear that biological medicines are both individual and complicated. Any pathway must take into account the fact that biological medicines are distinctly different from chemical drugs or we will fail in our responsibility to ensure patient safety and product efficacy.

Characterization Doesn't Tell the Whole Story

Biological medicines are complicated – but we have a long track record showing that they can be developed and characterized, and all the same tools are available for the development of follow-on biologics. However, while some of the best known peptide molecules – like insulin – can be largely characterized with today's technology, we do not yet have the tools and models that enable us to predict safety and efficacy from that characterization without undertaking human clinical trials.

Any pathway should fully address the patient safety considerations of medicines that are "similar to" or "comparable to" instead of "same as" the reference product. Given that proposals currently before Congress go far beyond the science in an effort to deem products having "minor differences in amino acid sequence" as "highly similar," I would like to share with you an experience we had at Novo Nordisk with two potential therapeutic proteins with just one amino acid difference.

Case Study: Minor Differences Can Have Major Health Consequences

Our goal was to create a fast acting insulin analogue that would enable patients with diabetes to use the medicine in close connection with a meal to control mealtime rise in blood glucose (and thus ease the

problem of too much or too little insulin at mealtime - a regular patient safety issue prior to the advent of the fast acting insulins). To pursue this goal, Novo Nordisk's strategy was to make a change in the amino acid sequence. We developed a number of drug candidates that were put into an extensive chemical, preclinical and clinical program. The candidate that we took to the market has only one change to the amino acid sequence from its precursor: in position B28 threonine is exchanged for aspartic acid. This change has resulted in an analogue (NovoLog) with significantly shorter time of action than human insulin (Novolin® R) and a unique safety profile. Significantly, an earlier candidate, also with only one amino acid substitution, similarly showed a positive effect on the timing of action but in full pre-clinical animal toxicological studies, this drug candidate also created a significantly increased tumourigenic (tumor growth response) potential in rats. This led to a decision by Novo Nordisk to immediately discontinue this program. As this experience shows, a seemingly "minor" difference can have enormous consequences for important safety characteristics.

Preclinical and Laboratory Tests Not Sufficient to Determine Immunogenicity and Other Issues

Mr. Chairman, this leads me to my next point. Based on our experience as I'll describe below, we believe clinical data is necessary to ensure that a follow-on biologic is safe. We are not advocating for a full package similar to that required of innovators, but comparable clinical data, albeit abbreviated, should be required to ensure drug safety.

In 2002, Novo Nordisk approached the FDA about creating a second generation manufacturing process for our fast acting insulins. Such upgrades are important because they ensure that our manufacturing technology processes are up-to-date and that our production capacity is adequate to meet demand. The changes involved in creating this second generation process included the use of a new precursor DNA; a new production strain and cell bank of the original host cell (*S.ccerivisiae)*; optimized fermentation, recovery and purification; and a new complete production facility. Any follow-on biologic manufacturer would have to do no less than (and most likely significantly more) to develop their unique manufacturing process than what was included in this undertaking for Novo Nordisk.

In order to implement these changes, the FDA required us to supply comparability data (comprising quality data on the structure, impurity

profile, stability and in-process characteristics), and clinical data encompassing phamcokinetics/pharmacodynamics (PK/PD) data as well as human immunogenicity data. To clarify, immunogenicity is how our body naturally responds to foreign substances – by developing antibodies. In our discussions with the FDA, they expressed confidence in our ability to detect and characterize impurities in this newly constructed medicine. However, FDA stated that no general safety threshold, even one as low as 0.1%, could be applied for new impurities because proteins can be immunogenic at very low concentrations and it is not known when "low" is "low enough." Because the immunogenic potential of a protein cannot be predicted from laboratory or preclinical investigations, the FDA required immunogenicity data from an appropriate clinical study. In response, Novo Nordisk submitted data showing comparable immunogenicity between the new and the older processes in a study of several hundred patients.

FDA Authority Should Not Be Constrained

Another example that may assist the Committee in their evaluation of how to establish a pathway that ensures that potential follow-on therapeutic proteins are both safe and effective can be illustrated by

the challenges Novo Nordisk faces in the investigation of a second generation process for the production of rFVIIa, a coagulation (clotting) factor used for the treatment of hemophilia patients with inhibitors. By moving from the current mammalian cell line derived from baby hamster kidneys to one derived from a Chinese hamster ovary (CHO) cell line, a more robust cell line for large scale manufacturing will be obtained.

At an early process step we identified a low level impurity (well below 0.1% in the drug substance) from the CHO cell line, which we proceeded to isolate and characterize. When we tested our experimental rFVIIa material in a repeat dose animal toxicity study we found a large number of animals developing antibodies directed against this impurity, indicating that it was very immunogenic in monkeys. Because this impurity is a foreign protein both to monkey and man, it implied a significant risk that our new product could lead to similar immunogenicity in humans with potential safety implications. Therefore we implemented additional process steps which succeeded in reducing this impurity to extremely low levels.

This example points out the need for the FDA to have the authority to require any safety studies it deems necessary to protect the public

safety. The fact is that a follow-on manufacturer, even after characterizing a product, would have a different cell line from the innovator, different processes, different raw materials, and no matter how well characterized, would not be able to be sure of the immunogenic effect of its product without clinical trials. Imagine the impact on patient safety if a follow-on manufacturer took a product to market not realizing that there were such impurities in the product from the host cell – and had not done clinical trials because Congress had not allowed FDA to require it.

Indeed, when we discussed this cell change program with the FDA at a pre-IND meeting, the FDA made it clear that rFVIIa produced in the new host cell line would be seen as a new product, which would need to stand on its own quality, safety and efficacy documentation including substantial clinical work and requiring submission of a full new BLA.

Multiple Indications Require Appropriate Data

Congress should reject proposals that would give a follow-on biologic based on a limited comparative clinical trial in one indication all indications of the innovator. Safety issues in different patient

populations treated with the same drug are not necessarily the same. RFVIIa® serves as a useful example here. RFVIIa® is a coagulation factor – meant to stop bleedings – and hence events associated with excessive clotting or formation of thrombi (blood clots) pose potential safety concerns. The risk of thrombus formation in a population of hemophilia patients with inhibitors (for which the product is approved) can be very different from the risk for patients with a normal coagulation system (for which the product has been/is being investigated in clinical trials). Similarly, the safety concerns for growth hormone treatment of children with growth hormone deficiency are different from those for adult patients with AIDS wasting for which growth hormone is also indicated. Because of the nature of the underlying conditions, subtle differences between a follow-on and innovator product that may not be evident in one patient population (i.e., may be considered a "minor" difference in that group of patients) may express itself more dramatically and detrimentally when the follow-on product is administered to a different patient population. Furthermore, adequate clinical and post-marketing safety experience in the use of a product in any indication should be established with the innovator product before a follow-on version (with reduced amount of safety data) can be approved.

Current Science Doesn't Support Interchangeability

Because of the potential difference in immunogenicity and other drug-specific adverse events, and because a follow-on biologic product cannot be determined to be the same as the innovator product, these products should not be allowed to be interchangeable. The European system recognizes that "by definition similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established." *(Guideline on Similar Biological Medicinal Products (CHMP/437/04))* There is a further requirement that the products are clearly identified to support post-market monitoring. In addition, there is no evidence to support interchangeability in existing biologics, let alone a new class of biologics with different safety standards. For example, there are currently three different companies who manufacture 9 different types of insulins in 23 different presentations – and they are not interchangeable. Indeed, the FDA expressed its concerns with interchangeability in September, 2006: "With protein products, as of today, the FDA has not determined how interchangeability can be

established for complex proteins. 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.htm)*

Traceability Important to Protect Safety

Congress should also carefully consider the issues involved in traceability, as Europe has done. Because these products are similar, but not the same, all protein drugs should be prescribed and given to the patient based on a unique name. To reference the regulations implemented in Europe, "in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified." *(Guideline on Similar Biological Medicinal Products (CHMP/437/04))* Different names will underscore that the products are, indeed, not "the same" and will help prescribers and dispensers avoid mistakes. Even extensive pre-approval clinical testing may be insufficient to detect rare, but potentially serious, side effects including immunogenicity. Such effects are often specific to one product but not another. Assurance of safety depends, even more than for typical small molecule drugs, on pharmacovigilance and other

post-marketing surveillance measures which allow the tracing of adverse events to a specific product – all of which are much more difficult if products from different manufacturers bear the same name (e.g. USAN or INN).

Conclusion

In summary, our experiences at Novo Nordisk have repeatedly shown that even small impurities or differences in molecular structure can lead to very important changes in properties of the product. These changes are not always detectable by standard analytical methods or predictable by animal tests, and therefore going beyond simple bioequivalence studies and requiring appropriate clinical investigations to document safety in patients is necessary.

Members of the Committee, the development of a follow-on biologics pathway is a complicated issue because of the significant scientific and public health issues involved. However, Novo Nordisk believes a pathway for follow-on biologics is possible provided it is rooted in the best science, preserves innovation of life-saving medicines for millions of patients across the globe, respects proprietary information, and

most importantly is constructed to protect patient safety. Novo Nordisk stands ready to assist Congress as this issue moves forward.

Additional Statement of
Inger Mollerup
VP for Regulatory Affairs
Novo Nordisk A/S
Committee on Oversight and Government Reform
March 26, 2007

Considerations for applying comparability concepts and comparability protocols for the development of follow-on biologics:

Comparability protocols and comparability guidelines (ICH as well as FDA) are designed for manufacturing changes in a process after approval. Based on existing experience with the process, the manufacturer develops a plan for the desired process change including an assessment of how such a process change may impact important product characteristics. Data is generated with the modified process from the step where the change is being implemented and all the way to the final drug substance or drug product. For example in a 15 step process, if a change is being implemented at step 4, analytical data will be compared for each step from step 4 (where the impact of the change on impurities etc. is normally largest) and onwards, all the way to step 15. In addition, stability profiles will be compared as well other process validation data. Thus, a very comprehensive set of data exists to support the change. *Although such a data set will be very comprehensive, and although characterization and analytical tools in general have higher sensitivity to detect differences than clinical studies, our experience nevertheless is that clinical data is required to support very substantial manufacturing changes such as change in cell substrate, a 2nd generation process or new formulation. Characterization does not tell the whole story – we do not yet have the tools and models that enable us to predict safety and efficacy from that characterization without undertaking human clinical trials.*

A follow-on producer can only compare his product to the innovator product which is available on the market, in its final formulation as intended for use. This can be analyzed and characterized thoroughly, and it can be assessed that overall structural features and purity profiles are comparable. However, low level impurities (significant only at earlier steps in the process) can not necessarily be identified in the final product, both because they may be present in concentrations below the detection limit, and because methods specific to the

individual impurity are needed to detect some types of impurities and prior knowledge about these impurities is therefore needed to develop the methods. A comparability assessment between a follow-on and an innovator protein based on analytical and chemical characterisation only is therefore significantly reduced compared to a full innovator comparability program, and additional nonclinical and clinical comparative studies are needed to ensure that minor differences between innovator and follow-on protein still result in comparable safety and efficacy in patients.

Chairman WAXMAN. Thank you very much, Ms. Mollerup.

Dr. Venkataraman, we are pleased to have you with us.

STATEMENT OF GANESH VENKATARAMAN

Mr. VENKATARAMAN. Good morning, Chairman Waxman and members of the committee. I want to thank you for the invitation and opportunity to present to you this morning on this very important topic to our industry and for the general public.

I am Ganesh Venkataraman, co-founder and senior vice president of research at Momenta Pharmaceuticals. I am pleased to come before you today to discuss the scientific issues behind the need to create an abbreviated regulatory approval process for generic biologics, which are defined as follow-on protein products in Dr. Woodcock's testimony.

The terms that I use are also defined in the written testimony that we are submitting for the record.

Mr. Chairman, I am a chemical engineer by training, with specific expertise in bioprocess engineering, protein structure characterization, and analytic and quantitative methods for categorizing complex mixtures. While at MIT I, with Dr. Sasisekharan and Dr. Langer developed novel analytic technology that enables characterization of complex mixtures. With this platform and co-science and leadership at MIT, we founded Momenta. We develop novel drugs and generic versions of complex products. We use cutting edge science to develop affordable and safe generic versions of these products.

Momenta has a strong interest in ensuring that Congress acts this year. We believe our company's experience demonstrates that the science is available today and continues to evolve to enable generic versions of complex mixture drugs.

In my written testimony I focused on five major issues that I will briefly discuss today.

First point, complex biologics can be totally characterized. Not all biologic products are the same, so when we discuss the characterization challenges we must keep in mind the continuum of complexity. Analytic technologies are here today to characterize the less-complex biologics, and approaches like ours and others are actively being developed for those that are more complex.

In my testimony I highlight how our testimony is applied to heparins. While heparins are not biologics, it validates how complex mixtures can be characterized.

The second point is: with such product characterization, generic companies will be able to design and control the manufacturing process to reproducibly make biologic drugs with the same quality as the branded companies. The manufacturing process for biologic drugs does not occur in a random or uncontrolled system. The living cells are highly specialized systems which, in a very careful and controlled manner, produce a final product.

Scientific advances in analytical technologies available to the generic as well as the branded industries allow one to link process parameters to the final product. It is possible and absolutely critical that generic companies build and maintain the same level of process knowledge.

Point three: clinical studies, ranging from small-scale PK to clinical outcome studies, should be used to address any residual uncertainty answering relevant scientific questions. Traditional empirical or full-scale clinical trials must not be a requirement for approval in all cases. While the FDA may require full-scale trials for approval of some biologics, others that have an increased level of characterization data should require significantly reduced clinical testing.

We believe FDA is well equipped to work with applicants to determine the degree of testing necessary and define the characterization and trial requirements.

Point four: biologic drugs can be designed to be interchangeable. Interchangeability is an important public health objective and products need to be designed and proved to be interchangeable. It is well within the reach in the near term for a number of products. This can be done through total characterization and/or through a proper combination of characterization and clinical trials.

Point five: patient safety and product quality will not be jeopardized. We should hold the entire industry, branded and generic, alike, to the highest scientific standards, and allow the expertise of FDA's scientific staff, which will approve and oversee the marketing of innovator and generic biologics.

In closing, Mr. Chairman, there is an opportunity to drive continued scientific innovation by creating a forward-looking, regulated system which balances the respective roles that characterization and clinical data should play. FDA has to be given the opportunity to make the decisions on comparability, which is interchangeability based, on the science presented to them. If legislation does not allow for such a pathway today, scientific innovation from technology companies like ours and many others will be stifled, and access to more-affordable choices would be denied.

I hope that my perspectives will be instructive to this debate. I am confident that these efforts under your leadership will be a key contributor to increasing access to safe, effective, and affordable medications to patients in need.

I thank you again for the opportunity to submit testimony. I look forward to answering any questions.

[The prepared statement of Mr. Venkataraman follows:]

STATEMENT OF

GANESH VENKATARAMAN, PH.D.

MOMENTA PHARMACEUTICALS, INC.

BEFORE THE HOUSE OF REPRESENTATIVES COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

HEARING: "SAFE AND AFFORDABLE BIOTECH DRUGS – THE NEED FOR A GENERIC PATHWAY"

MARCH 26, 2007

Good morning Chairman Waxman and Members of the Committee. I want to thank you for the invitation and the opportunity to present to you this morning on this very important topic to our industry and for the general public. I am Ganesh Venkataraman, co-founder and Senior Vice President of Research at Momenta Pharmaceuticals, Inc. Momenta is a young biotechnology company, founded in 2001, and based in Cambridge, MA with core science and leadership from the Massachusetts Institute of Technology. I am pleased to come before you today to discuss the scientific issues behind the need to create an abbreviated regulatory approval process for both biosimilar (comparable, and non-interchangeable) and biogeneric (equivalent, and interchangeable) drugs.

As an American citizen, I care about this at both personal and professional levels. As a biotechnology company that specializes in the characterization of complex mixtures, such as the complex protein drugs highlighted by today's hearing, Momenta has a strong interest in ensuring that Congress acts this year to provide a viable regulatory pathway for bringing safe and effective biosimilar and biogeneric drugs to market. Not only do we have products in development that would be adversely affected by inaction, but there is a strong public policy imperative for increasing access to safe and effective medicines. Moreover, we believe our company's experience demonstrates that the science and technology are available today to enable generic versions of complex mixture products. Establishing a safe and effective pathway also has the potential to drive continued scientific innovation from companies like ours and others by creating a flexible framework which allows the U.S. Food and Drug Administration (FDA) to make approval decisions based on the highest scientific standards.

Mr. Chairman, my comments here today will be limited to the scientific issues around creating such a regulatory framework as science is my core area of expertise. I will leave comments regarding specific policy, regulatory, or legislative process issues to my esteemed other panelists.

Background

By way of introduction, let me provide some background on Momenta Pharmaceuticals as well as my own professional experience. Momenta has an R&D pipeline that is somewhat atypical for a biotechnology company in that it includes both complex generic as well as novel drug candidates. Our product development efforts leverage our core technology expertise which is focused on the characterization, or thorough qualitative and quantitative analysis, of complex mixture drugs. Momenta's complex generic portfolio includes four complex mixture drugs: a complex polysaccharide mixture drug, a complex peptide mixture drug, and two glycoprotein mixture drugs. We also have a novel drug discovery and development program, where our lead product candidate is a rationally engineered anticoagulant, which is currently in Phase I clinical trials.

Prior to joining Momenta, I was a member of the research faculty at the Massachusetts Institute for Technology (MIT), where I studied the biochemistry and biophysics of complex molecules with a focus on complex carbohydrates, or sugars. I am a chemical engineer by training, having received both my MS and PhD degrees at MIT, with specific expertise in bioprocess engineering, protein structural characterization, and analytic and quantitative methods for characterizing complex mixtures. While at MIT, I, along with my colleagues Robert Langer and Ram Sasisekharan (both tenured professors at MIT), developed a novel analytical technology platform targeted at characterizing complex mixtures. With this platform as our foundation, we founded Momenta Pharmaceuticals.

Our initial research at MIT focused on analyzing and engineering complex sugar mixtures in order to better understand the role they play in human disease and pharmaceutical medicines. Sugars are one of the fundamental building blocks of human biology as linear sugars coat every cell in the human body and affect critical cellular interactions as well as the regulation of multiple disease states. Moreover, many complex drugs, including the biologic drugs which are the focus of this legislation, are glycosylated (i.e., complex sugar structures are attached to the surface of the protein backbone). This glycosylation adds significantly to a molecule's structural complexity and affects many of its biological and clinical attributes.

The presence or absence, and the degree of glycosylation (i.e., how many sugar structures are attached to the protein) is a frequent delineation between simpler and more complex protein products.

While sugars' role in biology has been well documented in scientific literature, advances in biologics have been impeded by a lack of understanding of the chemical structures of these heterogenous molecules. Specific to this debate, the inability to thoroughly characterize complex molecules has been cited frequently as a barrier for creating a pathway for generic biologics. Momenta is developing the analytical technology platform necessary to make this type of characterization a reality. Our goal in this debate is to highlight the latest innovations in science and the potential applicability of recent technological advances to help unlock the challenge of creating biogeneric and biosimilar versions of biotechnology products.

Introduction

We believe that any regulatory framework that is established has to be flexible and provide for the approval of both biosimilar and biogeneric products. There is an opportunity to drive continued scientific innovation by creating a forward-looking regulatory system, which balances the respective roles that characterization, preclinical, human clinical, and other scientific data should play in the approval of biosimilar and biogeneric products.

In addition, the FDA has to have the opportunity to make decisions around interchangeability based on the science presented to them. Interchangeability refers to specific designations provided by the FDA which enables pharmacists and other medical professionals to substitute one product for another. Currently, most traditional generic products are interchangeable with their branded counterparts and provide equivalent therapies at reduced cost. While interchangeability may not be possible for most biologics today, it is well within reach in the near term for a number of products. It is absolutely essential that legislation enable a regulatory pathway which provides for interchangeability, which will maximize needed and significant healthcare savings so important to patients. If legislation does not allow such a

pathway today, scientific innovation from technology companies like ours and many others will be stifled. The incentive to innovate will simply not be there.

I will focus my specific comments today around 5 major topics which have been consistently raised in different forums. In my discussion, I hope to highlight the state of science today and counter some of the rhetoric that has been posed by opponents of a proposed abbreviated regulatory pathway for generic biologics. These 5 issues are:

1. Product Characterization:
    - Myth: Complex biologic products can never be fully characterized.
    - Response: Analytical technologies exist today and are already being used to enable thorough characterization of complex mixture products.
2. Process Characterization:
    - Myth: Generic companies will never be able to develop the critical knowledge and strict control of the manufacturing process necessary to reproducibly make biologic drugs with the same quality as the branded companies.
    - Response: Analytical technologies can enable a thorough understanding and control of the manufacturing process to produce high quality complex mixture products.
3. Clinical Trials:
    - Myth: Full scale clinical trials must be required for approval in all cases.
    - Response: The extent of clinical trial data required for the approval of a biosimilar or biogeneric complex product should be determined by the FDA on a product-by-product basis. In general, it is inversely related to the level of process and product characterization that is available. This standard would be consistent with the current approach taken by FDA when an innovator makes manufacturing changes to a novel biologic product.
4. Interchangeability:
    - Myth: Biologic drugs can never be interchangeable.
    - Response: Either through thorough characterization, or through the appropriate combination of characterization and clinical trials, it is possible for complex

biologic products to be equivalent and interchangeable with the innovator product.

5. Patient Safety and Product Quality:
    - Myth: Patient Safety and Product Quality will be jeopardized.
    - Response: By holding the industry to the highest scientific standards and relying on the experience and expertise of FDA's scientific staff (which review, approve, and oversee the marketing of innovator, biogeneric and biosimilar products), patient safety and product quality will not be compromised.

I would like to provide my scientific perspective on each of these issues in more detail, based on my experience at MIT, as well as work which is actively ongoing at Momenta. We, like others, are focused on achieving a better understanding of these complex biologics, what they are and how they are produced, to enable the development and commercialization of the highest quality biogeneric and biosimilar products needed by the public today and in the future.

Myth #1 – Complex biologic products can never be fully characterized.

Definition of Complex Mixture Drugs: First, we should agree on the definition of a complex mixture drug. We are most familiar today with small molecule drugs, which exist as simple chemical structures, that are synthetically derived. These small molecule drugs can be chemically characterized and are readily manufactured through comparatively simple chemical synthesis. Complex mixture drugs, in stark contrast, are much larger, heterogenous mixtures, consisting of many structurally unique molecules. These unique molecules differ in their chemical structure and abundance within a mixture, are all biologically active, and dictate a drug's overall physiological and clinical profile. While there are many complex mixture drugs, the most common are the biologic drugs (i.e., therapeutic proteins, which are produced by living cells and organisms), which is the focus of this hearing.

Biologic Drugs Vary in Complexity: It is important to note that not all biologic products are the same. While each consists of multiple unique proteins, their complexity is also dictated by the number and type of glycosylation sites (i.e., how many sugar structures are attached to the surface of the protein backbone). Human growth hormone, for example, is a non-glycosylated protein (i.e., there are no sugars attached to the protein backbone). In contrast, interferon beta has one glycosylation site, whereas erythropoietin has four glycosylation sites. When we begin to discuss the challenges of characterizing these complex biologic mixtures, we must keep in mind this *continuum of complexity*. While characterization challenges exist for the more complex biologic products, analytical technologies are here today to enable the thorough characterization of some of the less complex biologic drugs.

Low Molecular Weight Heparins – A Case Study: I would like to review our experience with low molecular weight heparins (LMWHs), which I feel will highlight how far science has advanced and also help you understand where science is moving in this field. This class of compounds are anti-coagulants, and include marketed products today such as Lovenox®, Fragmin®, and Innohep®, all of which we have worked on in our laboratories at Momenta.

LMWHs are commonly used in the treatment and prevention of Deep Vein Thrombosis, and the treatment and management of Acute Coronary Syndromes. LMWHs are derived from pig intestines, which are carefully purified and treated (following a number of key manufacturing process steps) to produce the final product. LMWHs are complex heterogenous mixtures of hundreds of different unique molecules. These molecules are linear "sugar" chains, which vary in length and also in structural complexity (i.e., the structure and arrangement of the different sugar building blocks). In order to produce an equivalent version of any one of these LMWHs, we have to develop an analytical technology platform which would allow us to thoroughly characterize the innovator products. We have successfully developed and fine tuned such an analytical approach to enable the thorough characterization of these complex mixtures. This approach requires multiple analytical methods and an extensive bioinformatics integration of the resulting data sets, and allows us to structurally identify and quantify the various molecules in the mixture, fully capturing the micro- and macro-heterogeneity which dictates overall physiological profile and clinical outcome in patients. By characterizing

multiple samples of a given LMWH product, we are also able to understand and quantify the variability inherent in the innovator product, as a result of the manufacturing process. This allows us to set the appropriate "goal posts" (or equivalence window) which we can target to reproducibly make an equivalent version of the innovator product.

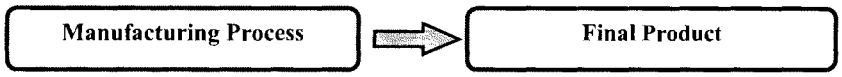
Biologics, which are produced by living cells, represent a new and different challenge. However, biologic drugs are also mixtures of many unique molecules, which vary in structure and abundance within the final mixture. Whereas LMWH products are mixtures of linear sugar chain molecules, biologic drugs are mixtures of protein-sugar molecules. The analytical approach we have applied to LMWHs can and is now being applied to these complex biologic drugs today. Analytical technologies are already here today to characterize the less complex biologic drugs, and approaches like ours and others are actively being developed which will make thorough characterization of the more complex biologic drugs a reality in the near future. While not possible for LMWHs only a few years ago, science has now advanced to allow for the thorough characterization of these complex mixture drugs. Thorough characterization of more complex biologic drugs will thus come sooner than we think, as scientific innovation continues to advance rapidly in this field.

Myth #2 – Generic companies will never be able to develop the critical knowledge and strict control of the manufacturing process necessary to reproducibly make biologic drugs with the same quality as the branded companies.

Understanding the Manufacturing Process: As I discussed earlier, biologic drugs are produced by complex, living organisms. This brings an obvious added level of complexity to the manufacturing process over the simpler chemical manufacturing processes which are practiced for small molecule drugs. However, it is important to acknowledge that the manufacturing process for biologic drugs does not occur in a random, or uncontrolled "system". First, a cell produces a certain protein. Then, the cell modifies the protein in many ways, for example by adding selected complex sugar molecules to the protein backbone, which can produce changes in conformational structure and design. These latter changes are often called "post-translational modifications". Thus, these living cells are actually highly

specialized systems which in a careful, and very controlled manner, produce the various molecules that constitute the final biologic mixture. As practiced currently by the innovator, analytical technologies can be utilized to understand the manufacturing process and its intricate relationship with the final product. It is possible, and will be absolutely critical that the generic company and contract manufacturers also build and maintain this same level of process knowledge. With tools such as those that Momenta and others are developing, even innovator companies may be able to better control their manufacturing process in the future.

Low Molecular Weight Heparins – A Case Study: Again, I would like to use our internal work with LMWHs to highlight the value of building a process-product relationship for a complex mixture drug. As I discussed earlier, LMWHs are derived from pig intestines, via cells which biosynthetically produce the heparin starting material needed for the manufacturing process. As we are able to fully characterize a given LMWH product and define its inherent variability, we can determine the "goal posts" which we need to target to ensure we can make an equivalent version of a LMWH product. With such an analytical framework in place, we can carefully study and understand the impact of the starting material (the pig intestines or porcine mucosa, and the final purified heparin), and the critical steps in the manufacturing process. Following a careful, step-by-step approach, we can reverse engineer the manufacturing process, build a strong knowledge and experience base with our process, and determine the critical elements we need to control to ensure that we can reproducibly make an equivalent version of a LMWH product. In simple terms, we need to understand which "dials" are important to turn in the manufacturing process, and appropriately adjust and control these "dials" to ensure a quality product time and time again. The figure below highlights the critical relationship between process and product.



Process Characterization
- *process knowledge and understanding of starting material and process parameters*
- *process engineering*
- *process quality and control*

Product Characterization
- *identify and quantify the molecules which comprise the mixture*
- *define variability in innovator product*
- *determine "equivalence window" for complex generic product*

This same approach can be applied to biologic products. There is a certain predictability to how cells produce the protein backbone and modify this backbone to produce the final product. This is not a random, uncontrolled system. Scientific advances in analytical technologies, available to the generic as well as the innovator companies, make this type of process knowledge and understanding a reality for some simpler biologics today and will make it possible for other, more complex biologics in the near future.

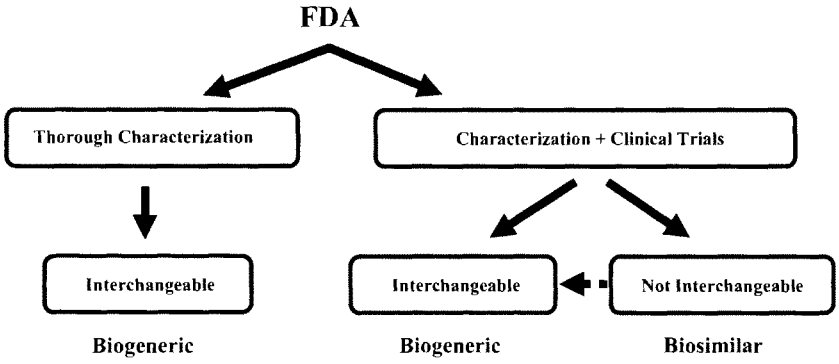
Myth #3: Full scale clinical trials must be required for approval in all cases.

Here again it is important to acknowledge the continuum of complexity of biologic drugs. The level of characterization data will allow the FDA to determine the extent of clinical testing which will be necessary for approval. While FDA may require full scale clinical trials for approval of some biologic products, significantly reduced clinical testing requirements (i.e., smaller scale clinical studies assessing bioequivalence, immunogenicity, or more targeted clinical endpoints) will be required for the approval of other biologic products due to the increased level of characterization data which is provided. We are establishing the feasibility of, and are working toward the characterization tools which will demonstrate equivalence to innovator product and manufacturing control. This thorough characterization will ensure the biologic products produced can be relied on to produce the same clinical result as the innovators product in a given patient without the need for extensive clinical trials. We believe the FDA is well equipped to work with applicants to determine the degree of testing necessary

and believe any legislation should enable a substitutable pathway and leave the definition of characterization and trial requirements to the FDA.

Myth #4: Biologic Drugs can never be interchangeable.

FDA must have the freedom to evaluate each application and make the appropriate determination of comparability versus interchangeability. As the diagram below presents, we support the creation of both a biogeneric and biosimilar pathway.



We see three distinct regulatory pathways to enable the approval of biologic products. In the near term, due to the complexity of most of these biologics, most applicants will pursue a biosimilar regulatory path, based on a combination of characterization and clinical data. Particularly for less complex biologic drugs, and with the continued advancement of analytical technologies, some applicants will also pursue a biogeneric regulatory path by providing sufficient characterization data, likely coupled with reduced clinical data requirements, to clearly demonstrate that its product will reliably produce the same clinical effects as the innovator drug in a given patient. Finally, while I recognize that thorough characterization is only possible today for the less complex mixture drugs, we feel it is critically important that a pathway which relies on thorough characterization, analogous to what we have today for small molecule drugs, also be authorized to drive continued scientific

innovation in this field. It is via the two biogeneric legislatively authorized paths, where the significant cost savings to the American public will become a reality.

Myth #5: Patient Safety and Product Quality will be jeopardized

The final issue I would like to highlight is the need to hold the entire industry, branded and generic alike, to the highest quality and safety standards as they bring new products to market. We believe that the standards for generics and novel drugs should be comparable and seek parity among the approval systems for these products. To this end, we encourage the development of a regulatory framework that provides FDA with discretion to produce appropriate guidance based on its own understanding of what is scientifically reasonable. We have collectively entrusted FDA with the authority to approve complex biologic products for years. We will rely on this same scientific team and expertise at FDA to make the appropriate science-based decisions for biogeneric and biosimilar approvals. With the appropriate application of the latest technology, patient safety and product quality will not be compromised.

Summary

In conclusion, I would like to restate our core beliefs on this issue.

- The tools for characterization of complex drugs are at hand. It is already possible to thoroughly characterize complex mixture products.
- Today's technologies can ensure reproducible and well controlled manufacturing processes which can deliver safe and reliable products in the hands of competent biologic manufacturers.
- Bioequivalence and safety for biosimilar and biogeneric products can be demonstrated through complementary sets of characterization analytics and where necessary, limited clinical trial data.
- Legislation that provides for interchangeable biogenerics is essential to provide the incentives for the industry to continue to invest and innovate in needed characterization and process control technologies. This is the single best way to

ensure the competition necessary to deliver these drugs safely and cost effectively to the patients that most need them.

- We should rely on FDA, which has been approving complex biologics for years, to ensure the highest quality and safety standards going forward.

Mr. Chairman, I want to thank you again for your leadership in raising attention to the need for a timely and responsive legislatively authorized pathway, which has the potential to make biogeneric and biosimilar medications a reality in this country. We believe it is critical for all of us that such a framework be created that is forward looking and enables science to drive our future direction. I hope that my perspectives have been instructive to this debate. I am confident that these efforts under your leadership will be a key contributor to increasing access to safe, effective, and affordable medications to patients in need.

I thank you again for the opportunity to submit testimony today and look forward to answering any questions you may have.

Chairman WAXMAN. Thank you very much, Dr. Venkataraman.

To begin the questioning, the Chair recognizes Mr. Burton.

Mr. BURTON. I thank the Chair for recognizing me. I have to go put a pharmaceutical in my eye at the hospital, so I can attest to the necessity for those products.

Mr. Chairman, I am not sure this question should be directed to the panel. It may be directed at you. From everything I have seen, there can be a minor difference in a biological product, and if the pharmaceutical company that created the product in the first place has to give a generic company the information before their patent expires, it seems to me, because of the minor difference that could be created by the generic company, they could apply for a license well before the patent runs out from the original producer. If that were the case, the scientific research being paid for by the original company, the pharmaceutical company that developed the product, could lose its investment after they have created something that is going to be beneficial to everybody.

So my question is: has that been checked out legally and whether or not the originating company can be protected for the duration of their patent?

Chairman WAXMAN. Perhaps we can let one of the panelists answer it, but it seems to me it becomes a patent question. If the originator of the product has a patent over that product, a minor variation, as you seem to describe it, would not be permitted as a competitor, if it is basically the same product.

Mr. BURTON. I think the bill has a great deal of merit.

Chairman WAXMAN. This is, of course, by the way, what we do right now with generics and brand name drugs. We allow generics to compete after the patent is over. If there is a new innovation in it or a minor difference, then the FDA would have to decide if it is, in fact, a generic.

Mr. BURTON. I understand that. I like the bill. That is one thing I would like to check out. Thank you, and thank you for yielding.

Chairman WAXMAN. Thank you very much.

The Chair recognizes himself.

Let me address this question to Dr. Gerrard and Dr. Schwieterman. As you testified, for over 10 years the FDA has allowed brand name manufactures of biotech drugs to make changes in the process by which they manufacture their products, but without repeating the original safety and effectiveness trials. This policy seems to me to undercut the brand name industry argument that changes in manufacturing processes can affect safety and effectiveness in ways that could only be assessed through clinical trials. In your judgment and experience, does permitting companies to make significant manufacturing changes under a comparability protocol, but without repeating clinical trials, adequately protect patients from unsafe or ineffective products?

Ms. GERRARD. I think, as both Dr. Woodcock and Dr. Schwieterman have said, FDA only has one standard for safety and efficacy, so when FDA makes the decision that, after a manufacturing change, that the product is comparable, they have decided that it is going to have the same safety and efficacy as the brand name product. What we are saying is some of those same principles apply to the development of generic biotech products.

Chairman WAXMAN. Yes.

Mr. SCHWIETERMAN. Yes, let me just add to that. The FDA is a science-based organization. It is filled with scientists. It is filled with physician reviewers. It is filled with people who are expert in data analysis and interpretation. Your question really is adking if the science there to allow in some cases for the absence of clinical trials, and I would say yes, it is there, but you would have to look at the data, you would have to look at the techniques, you would have to look at the actual agent under discussion. You take things on a case-by-case basis, based upon the science and the data, and then make that determination.

Chairman WAXMAN. Are there many examples of products approved under comparability protocols that turned out to have unpredicted safety or effectiveness problems that were only discovered after marketing?

Mr. SCHWIETERMAN. There are none in the United States where there were major changes in post-marketing that caused this. We all know the example of Eprex, which occurred post-marketing in Europe. The patients developed PRCA. But the agency and the biotechnology industry and biopharmaceutical industry in this country has been amazingly good at protecting the public this way.

Chairman WAXMAN. Does the scientific rationale underlying comparability protocols and FDA's 10 years of experience implementing it provide evidence that an abbreviated application process for follow-on proteins and biogenerics based on established comparability principles could adequately protect patients from unsafe or ineffective products? Dr. Gerrard.

Ms. GERRARD. I think the comparability policies have been enormously successful from FDA's point, and the American public has benefited, as well. Brand name companies have been able to make manufacturing changes and improve their product without the need to redo clinical trials.

I think we can apply some of those same principles in extending it one step further to generic biotech products.

Mr. SCHWIETERMAN. I would just like to add that I think the rationale is, in fact, one that can be used, coupled with the data, coupled with the case-by-case to develop a safe and effective biogeneric use of the principles we outlined.

Chairman WAXMAN. Dr. Schwieterman, Ms. Mollerup testified that immunogenicity can arise so unpredictably from changes in biologics that a follow-on biologic will always require a clinical trial to assess immunogenicity. When a brand name company uses the FDA's comparability guidance to make changes to its existing biologic products, are clinical trials always required to demonstrate that no new immunogenicity concerns have arisen?

Mr. SCHWIETERMAN. Always is an absolute, and absolutes are only things that can be supported by the data. FDA is a scientific organization, and I would say no. In every instance ought there be a clinical trial for immunogenicity? No. It would depend upon the nature of the case. It would depend on the data that are there. And I think there are ways and methods for sure beyond clinical trials to determine immunogenicity. In fact, clinical trials, themselves, have limitations in this regard, as they do with other infrequent safety AEs.

Chairman WAXMAN. Should there be more concern about immunogenicity for follow-on proteins than for brand name proteins?

Mr. SCHWIETERMAN. I don't think there should be more or less concern about immunogenicity. I think that the safety of all agents, particularly biogenerics and biopharmaceuticals in this country is a critical issue for the FDA. I think that the same standards, the same kinds of oversight, the same considerations for biogenerics ought to apply for them as they do for present-day biopharmaceuticals.

Chairman WAXMAN. Let me ask a question of Dr. Venkataraman and Dr. Allan. A number of companies have expressed doubts about whether copies of biotech drugs can be made safely. They have suggested that the manufacturing process for producing these drugs is so complex that new companies will not understand biologics manufacturing well enough to produce safe versions of these products. Isn't it true that there are a number of companies who already make brand name biotech drugs, either for themselves or on contract for other companies, who would be likely to want to make copies for biotech drugs if there were a legal pathway?

Mr. ALLAN. I believe there are contract manufacturing organizations that do make branded products, either at the research level, the development stage level, or even at the commercial level.

Chairman WAXMAN. Yes.

Mr. VENKATARAMAN. I would like to add I think the brand name manufacturers sometimes have made the process to be a black box. I think the science is there now to be able to go back and decouple product and relationship to the process so that you could use a different cell line and come up with a different process that would ultimately provide you the same end product. Provided you couple that with the characterization of looking at process-related impurities and end product, you could get there to the same level of being in a brand name manufacturer.

Chairman WAXMAN. Thank you very much.

Mr. Davis.

Mr. DAVIS OF VIRGINIA. Thank you, Mr. Waxman.

Ms. Mollerup, let me start with you. The generic system we created for pharmaceutical drugs in 1984, which bears Mr. Waxman's name, balanced and abbreviated approval systems for generic drugs with patent restoration and new exclusivity for innovators. Doesn't such a critical balance continue to stimulate the development of new cures for drugs, having that balance?

Ms. MOLLERUP. In my mind it is important that we keep the balance that will still foster innovation, and as this process goes forward toward defining a legislative and regulatory system, that is acknowledged, because you would still want new drugs to come on the market in this country.

Mr. DAVIS OF VIRGINIA. What kind of impact would a system that fails to assure safety or sustain innovator intellectual property rights have on innovation?

Ms. MOLLERUP. A system that would fail to protect safety I think would be detrimental for both innovation and follow-on manufactures, and obviously first and foremost for public health. I think it is very important, as Congress moves forward, that the pathway

you are moving toward is really constructed to protect patient safety and be rooted in the best science, and there is a lot of strong and good science available for this.

Mr. DAVIS OF VIRGINIA. The FDA stated in its testimony that demonstrating the similarity of a follow-on protein product to a reference product is more complex and would require new data. I guess my question is: does this mean FDA should require clinical safety data for follow-on biologics, or do you think there are cases where they could make the determination it wouldn't?

Ms. MOLLERUP. Based on my experience with those complete second-generation processes that we have developed and are developing at Nova Nordisk, these require immunogenicity data in all cases for the simpler ones like insulin, described in my testimony. Besides that, PKPD was required to assess both pharmacokinetics and efficacy for a more complex one like a co-correlation factor, substantial clinical data will be required, as well as immunogenicity.

So, based on the experience that we have with processes that have less substantial changes than follow-ons, from my standpoint, where the science is today, immunogenicity trials will always be required.

Mr. DAVIS OF VIRGINIA. Thank you.

Let me ask Dr. Venkataraman and Dr. Allan, you are both from small biotech companies. FDA stated in their testimony that technology today is not yet sufficient to allow for comparisons of complex protein products. Do you agree with that?

Mr. ALLAN. Well, it has to be viewed on a case-by-case basis. I think for the product we developed the analytical methodology that we used, which was fairly extensive, was very adequate to demonstrate the structural characterization of the property.

Mr. DAVIS OF VIRGINIA. DO you think it depends?

Mr. ALLAN. It will depend on the products. There are some proteins that are fairly simple, relatively speaking, and you can characterize them extremely well.

Mr. VENKATARAMAN. I agree. I think on a case-by-case basis there are several proteins that can be characterized well today, and science continues to evolve. Academic groups and other companies I know are working very actively toward creating novel technologies to be able to do this for more complicated products. And I think a regulatory and a legal legislative incentive is going to propel that technology forward much faster to be able to do this much more sophisticatedly.

Mr. DAVIS OF VIRGINIA. How close are we, do you think? It is hard to say, I know, but a couple years, 10 years?

Mr. VENKATARAMAN. It is difficult to say, but 4 years ago, when we started working on our program, people thought it was impossible to do. We were discouraged extremely. Today we have an application, we have talked to the FDA. It has been completely solved. I think similar situations have been reported by other people. So it is a matter of providing the right incentives for the scientists to be able to take it on.

Mr. DAVIS OF VIRGINIA. OK. Are there any non-clinical tests or technologies that could fully substitute for studying the safety of biotech products in humans?

Mr. VENKATARAMAN. I would say that the safety, per se, so the comparability of the two products, characterization becomes a very important aspect of knowing how close you are to the innovator product. I think there are multiple analytical techniques that provide you very rigorous estimation of the product quality and product attributes, so yes.

Mr. DAVIS OF VIRGINIA. All right.

Let me ask Dr. Schwieterman and Ms. Gerrard, the FDA highlighted in its testimony the importance of ensuring that facilitating the development of follow-on product through abbreviated pathways doesn't discourage innovation and the development of new biological products. They also refer to the Hatch-Waxman Act as a balanced approach. Do you think an extension of data exclusivity period and certain patent protections would help encourage innovation and development with biological products?

Ms. GERRARD. I am not a lawyer. I am a scientist. I guess I have confidence in the innovation of biotech companies that I work with to continually come up with new and better products.

Mr. DAVIS OF VIRGINIA. All right. From a scientific point of view it is achievable, but from a policy point of view you are going to take a pass on it?

Ms. GERRARD. I am not a lawyer. I am a scientist.

Mr. DAVIS OF VIRGINIA. That is fine.

Mr. SCHWIETERMAN. I will take a pass, as well. I am a physician scientist. From a scientific point of view I agree with what Dr. Gerrard said.

Mr. DAVIS OF VIRGINIA. Well, Henry and I are both lawyers. Thank you.

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Yarmuth.

Mr. YARMUTH. Thank you, Mr. Chairman.

As a child I was left way behind on science, so I am going to pass on the science questions for a minute and ask something I know a little bit more about, and that is the business side of this, and I am asking business questions of a panel of scientists. I understand that.

Am I correct in assuming—and anyone can answer this—I take it, just reading between the lines, we have several representatives from generic manufacturing companies and one from a brand name company. Judging from what we have heard about the complexity of these biologic drugs as opposed to chemical-based drugs, and we all know the stories about how chemical-based drugs cost pennies apiece to produce and they are sold for whatever, but it seems to me that the economics of biologics are significantly different and more complex and therefore dramatically more expensive. If I am correct in that assumption and the process is inherently expensive, how much money can we save by producing them on the generic basis or follow-on basis as opposed to the brand name?

I guess a premise, we know that for Claritin and for Zantac and all these other products, and many of the drugs that are actually still by prescription, that we have a significant amount spent for advertising and marketing. I assume marketing, anyway, is still a big component of the biologics business. But what are we talking about, either from a historical perspective that you know about or

potentially that we are talking about saving by allowing these drugs to be produced generically?

Mr. ALLAN. I can give that a shot. Actually, I don't think anybody around this table is from the generic industry. Some of us are from the innovation biotechnology industry.

With regard to price, it is going to be a case-by-case basis. There is no doubt to make a complex protein is more expensive to make than a small molecule. The manufacturing facilities that are needed, the overhead, so to speak, that goes into the whole program is probably larger than the financial commitment you would want to make for a small molecule plant. So I think intrinsically it is a more expensive business, but I believe that, you know, certainly none of us would be sitting around this table if we felt that we couldn't make these types of products at a significant price reduction to the innovator product. It will be case-by-case. What would be the percentage reduction I don't think we could—I certainly would not comment on that right now, but, as I said, it will be less expensive.

Mr. YARMUTH. Go ahead.

Mr. VENKATARAMAN. I was just going to add one comment. I don't know if I can give you any numbers, but what I do know is that the margin between the cost to manufacture and the actual price is significant. I don't have exact numbers, but it is quite significant, and I assume that could translate into cost savings in the long run.

Mr. YARMUTH. Again, I understand I am asking business questions of scientists, but would the savings result, assuming that we allow an easier pathway to producing generics, would the savings result more from the competitive aspect, or would they result from the fact that, just because we have protected the brand name manufacturer, that we have allowed that price to be very, very high, and that just by eliminating the exclusivity we bring the price down? Would the savings be inherent? Would they be related to competition, or is it just because we are allowing exorbitant profits now, understanding that those profits are being allowed to allow the company to recover some of its investment?

Mr. ALLAN. I think it will be the introduction of competition, to a certain extent.

Ms. GERRARD. And my economic knowledge might be right behind my legal knowledge, but I think what we have to understand is that, while biologics might be more expensive to make than drugs, that there is still a huge margin there, and that, while the cost savings, even conservative estimates that say 25 percent, which we have seen, when you consider that the cost of a biologic is so high that a 25 percent savings is a huge amount.

Mr. YARMUTH. You look like you want to answer.

Mr. VENKATARAMAN. The pricing for a drug that a company like Momenta would launch as a generic would be lower by at least 20, 25, 15 percent, depends on the dynamics, but because the lower prices of the drug I think the cost saving would be achieved.

Mr. YARMUTH. Ms. Mollerup, did you want to comment?

Ms. MOLLERUP. Yes. I mean, cost is an important consideration and I think that a lower cost of drugs is good, as long as it is not at the expense of patient safety. I guess, again, back to the need

for clinical trials, I would like to share with you, an example which I guess indicates somewhat where the borderline may be. In Europe we have not only had two approvals of follow-ons, but also one rejection. That was on an Interferon Alpha that did not show comparability in its clinical trial in that more patients had relapse of their disease after the treatment with Alferon was stopped, compared to the reference product, and there were also more side effects in the Alferon group. Again, I am not an economist. I am a scientist, but it just goes back to the equation of cost savings, that some cost savings can be realized but the products are expensive to produce, and as this example from Europe shows, care really has to be exercised as to make sure that the appropriate comparable clinical data, not a copy of the original data set that was handed in, but appropriate comparable data ensuring comparable efficacy and safety is included.

Mr. YARMUTH. Thank you.

Chairman WAXMAN. Thank you, Mr. Yarmuth.

Mr. Welch.

Mr. WELCH. Thank you, Mr. Chairman.

Dr. Gerrard, Dr. Mollerup argued that the risk of immunogenicity from a follow-on product must always be evaluated with clinical trials. That is my understanding of her testimony. In your view, are clinical trials the best or the most sensitive method of detecting this?

Ms. GERRARD. Not always. I think we have to keep in mind that immunogenicity, as I stated, a product having greater immunogenicity really is not an issue; it is when there are clinical consequences. Immunogenicity just means you make antibodies to the product. Most of the time they are not neutralizing. Many times they are temporary. Patients continue to be treated. So it is not always an issue.

Second, is clinical trial the best way to determine immunogenicity differences between two products? It may not always be the case. Sometimes more rigorous analytical comparisons, either an assessment of the product and product instability are really a much more sensitive way of determining whether that product is going to cause problems.

Mr. WELCH. Thank you.

Dr. Schwieterman, would you agree with that?

Mr. SCHWIETERMAN. Yes, I would. I think the concept of immunogenicity is one that has been talked about a lot, but, in fact, it is a quite complex subject. There are certain kinds of immunogenicities, then there are other kinds. We have had many day-long conferences about this. The ability of clinical trials to detect immunogenicity depends on what you are talking about. For most of the things that have been bandied about, actually clinical trials are rather poor measures for picking up the kinds of outcomes that you have heard.

Mr. WELCH. Thank you.

I would ask this question to both of you, as well. Opponents of the generic biological pathway, as you know, always raise the example of Eprex, Johnson & Johnson's European version of Epogen. Can you explain a little bit about what happened with Eprex? I will start, I guess, with you, Dr. Schwieterman.

Mr. SCHWIETERMAN. I don't know, of course, the data on the manufacturing changes that were made, nor was I privy to the investigations made. I know that Johnson & Johnson underwent a great deal of investigations. I mean, just to tell the story as I know from my standpoint, Eprex, which was one of the erythropoietin—ESAs, they are called, in general, erythropoietic stimulating agents—was marketed and approved overseas, and then cases of autoimmune disease or a very bad autoimmune immunogenic reaction to the drug, itself, ensued. In other words, the body started reacting to its own protein based upon that.

The thing about this particular case that is different is that, No. 1, it occurred overseas, so, you know, there was no real knowledge of whether the analytic tests that were performed there were adequate or complete and whether they would have been picked up at the FDA.

No. 2, the ultimate investigation into this product, as I understand it from Dr. Segal's testimony several weeks ago, picked up on impurities that are actually determined with analytic tests after the fact, and most of the investigation ensued upon that; that is to say, the actual analysis of the product, itself.

From my vantage point, it is clearly an important issue, because we need to understand it, but it doesn't visciate, it doesn't make the arguments about analytic tests weaker, in my estimation. In some ways it makes them stronger.

Mr. WELCH. Go ahead, Dr. Gerrard.

Ms. GERRARD. I was just going to add to that. Pure red cell plasma is a very serious disease, but it occurred in 1 in 10,000 patients. So could this have been detected in a typical clinical trial of, say, several hundred people? No, it could not. What actually did resolve the issue for Johnson & Johnson's Eprex was a more rigorous analytical characterization to resolve that problem.

Mr. WELCH. Thank you. How large a clinical trial would have been required to identify that side effect?

Ms. MOLLERUP. I think that everyone agrees it would have taken an extremely large clinical trial, and, from my perspective, the purpose of doing these comparative immunogenicity trials where you can, from the blood samples, isolate antibodies, characterize them, find out whether they are benign or not, and I fully agree with Dr. Gerrard that not all antibody responses are a safety issue.

But with the case of these comparable clinical trials to test immunogenicity, the real important point here is that such trials can tell us if there is a major problem. For innovator products, as well as for follow-ons, it is the long-term safety monitoring that is also needed in order to pick up on minor problems like this.

Mr. WELCH. How large a clinical trial would have been required, then, Ms. Mollerup?

Ms. MOLLERUP. I don't have the clinical for Eprex because I don't have that statistic, but, back to Dr. Segal's testimony, it would take a study of about 50,000 patients to have a good chance of detecting a serious effect in a patient, 1 patient out of 1,000. But I don't have the statistics on Eprex.

Mr. WELCH. And my understanding—anybody can answer this—is that Johnson & Johnson, itself, doesn't argue that the Eprex

problem would have been avoided, in fact, had they conducted a clinical trial before marketing the change product. Dr. Gerrard?

Ms. GERRARD. No, they would not have detected it in a clinical trial. Every product is subject to post-marketing surveillance.

Mr. WELCH. Right.

Ms. GERRARD. So a very rigorous post-marketing surveillance program is also important for every product.

Mr. WELCH. Dr. Schwieterman.

Mr. SCHWIETERMAN. One point I want to make is you don't conduct clinical trials for no reason. You are exposing patients to agents and putting them through a protocol and data collection and blood drawing and so forth to collect scientific data for scientific reasons that are pre-established in hypotheses, and so to argue that clinical trials should be conducted all the time is really to negate the basic premise of a clinical trial, which is the study of question.

In the case of Eprex, it would have been an impossibly large study to have studied that particular issue; therefore, a clinical trial not only would have been undetected, insensitive to that particular change; it wouldn't have offered any information at all.

Mr. WELCH. Just following on your point, would it make scientific sense to argue that the expressed example supports a clinical trial requirement for follow-on products but does not support that same requirement for brand name products?

Ms. MOLLERUP. I think, from looking at what is required for the brand name industry, I mean, the trials that we undertake, both phase two and phase three trials, immunogenicity is an obvious part of that program, because we are working with proteins and the immunogenetic profile of our products are also not established as we take them through the clinical program, so that is certainly part of the testing we do, as well.

Mr. WELCH. I'm not sure I understand you. You are saying that you have to have those clinical tests for the follow-on products but you don't have to have them for the brand name products?

Ms. MOLLERUP. No. I am saying the exact opposite. I am saying that we, in the brand name products clinical trials that we use to take these to the market, immunogenicity studies are an integrated component, and what we find reasonable to establish clinical comparability for the follow-ons is to also study immunogenicity in an appropriately sized comparative trial, and that will be a lot smaller than the innovator phase three studies.

Mr. WELCH. Dr. Schwieterman, go ahead.

Mr. SCHWIETERMAN. I guess I would disagree with that. Mandated clinical trials to study immunogenicity is not something that is scientific, but rather political. In this particular case, if the science is there, depending upon the drug, depending upon the question, the patient, and the test, you could do a clinical study in certain instances where you believed that information would be useful from that clinical study. But to mandate it for all studies would be to also perform it for those cases where it wouldn't be useful.

I think that what ought to happen is that the FDA, like they do now, be able to have the flexibility and the authority to use their

assessments of the data and the context of that data to make judgments about the need for further clinical studies.

Mr. WELCH. Thank you.

Dr. Gerrard, last word?

Ms. GERRARD. I will just add to that. I think FDA does need that flexibility. You look at the history of the product, have there been any clinical consequences to the immunogenicity? What about the analytical characterization? You look at the whole picture. If there are remaining questions, of course safety is paramount. We want FDA to have the ability to request any additional data that they need to make sure that product is safe.

Mr. WELCH. Thank you. I yield the balance of my time.

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

Dr. Mollerup, would you support giving FDA the ability to require and enforce post-market studies for both the generic and for the brand name drugs?

Ms. MOLLERUP. I am from Europe, so I have a fair amount of knowledge of the regulatory system here in the United States, but may not be accurate on all the details. From my perspective, the FDA should be able to put the same requirements to both innovators and follow-ons, because the same safety issues are involved.

Chairman WAXMAN. Right. In the United States the manufacturer agrees, when the product is licensed, to do followup tests for post-marketing, but they may not do it because there is not a sanction except to take them off the market, which has never been used. Do you think FDA should have the power to require post-marketing safety studies? You say it should be for both or either when it is necessary. Do you think FDA ought to have that power?

Ms. MOLLERUP. The power not only to ask for the data, but also actually to get it?

Chairman WAXMAN. And to insist it be done?

Ms. MOLLERUP. Yes, I think they should.

Chairman WAXMAN. Thank you.

Well, I thank all of you very much. You have been very helpful, and I appreciate your testimony. This may be self-serving, but the bill does allow FDA to require clinical trials. It allows FDA to do whatever is necessary to determine that the science indicates a generic version is safe and effective.

Thank you very much.

I want to call forward the witnesses for our third panel.

Yvonne Brown is an individual living with multiple sclerosis and is speaking today on behalf of the National Multiple Sclerosis Society.

Mary Nathan is an individual living with a rare disease called Gaucher disease, and is speaking today on behalf of the National Organization for Rare Disorders.

Nelda Barnett is a Board Member for AARP.

Priya Mathur is the vice chair of health benefits, Board of Administration, at the California Public Employees' Retirement System [CalPERS].

Scott McKibbin is the special advocate for prescription drugs for the State of Illinois.

Dr. Henry Grabowski is a professor of economics and the director of the program in Pharmaceuticals and Health Economics at Duke University.

Jonah Houts is a senior analyst at Express Scripts, Inc., a pharmacy benefit management company [PBM], representing 1,600 clients, including large, self-insured employers, government payers, unions, and health insurance companies, and covering more than 50 million people.

We welcome you all to this hearing today. Your prepared statements will be in the record in full. We would like to ask each of you to limit the oral presentation to around 5 minutes.

It is the custom of this committee, as you have already observed, having sat through the earlier panels, to ask all of the witnesses to be sworn in, so I would like to ask each of you to rise and raise your right hands.

[Witnesses sworn.]

Chairman WAXMAN. The record will indicate that each of the witnesses answered in the affirmative.

Ms. Brown, why don't we start with you, if you have the mic passed over.

The timer, by the way, will be green, and then it will turn to yellow for the last full minute, and then red when that last minute is up.

Thank you so much for being here.

STATEMENTS OF YVONNE BROWN, FOR THE NATIONAL MULTIPLE SCLEROSIS SOCIETY; MARY NATHAN, FOR THE NATIONAL ORGANIZATION FOR RARE DISORDERS [NORD]; NELDA BARNETT, BOARD MEMBER, AARP; PRIYA MATHUR, VICE CHAIR, HEALTH BENEFITS-BOARD OF ADMINISTRATION, CALIFORNIA PUBLIC EMPLOYEES' RETIREMENT SYSTEM [CALPERS]; SCOTT D. MCKIBBIN, SPECIAL ADVOCATE FOR PRESCRIPTION DRUGS, STATE OF ILLINOIS; HENRY GRABOWSKI, PH.D, PROFESSOR OF ECONOMICS, DIRECTOR, PROGRAM IN PHARMACEUTICALS AND HEALTH ECONOMICS, DUKE UNIVERSITY; AND JONAH HOUTS, SENIOR ANALYST, EXPRESS SCRIPTS, INC.

STATEMENT OF YVONNE BROWN

Ms. BROWN. Thank you, Chairman Waxman and distinguished members of the committee, for inviting me to provide testimony at this hearing, and thank you, Chairman Waxman, for your leadership on this issue.

My name is Yvonne Brown. I live in Waldorf, MD. I have multiple sclerosis [MS]. I am not a pharmaceutical company. I am not a lobbyist. I am simply a 44-year-old woman who struggles every day with the devastating effects of MS and the unaffordable cost of treatment.

MS is chronic, it is unpredictable, an often disabling disease of the central nervous system. It basically stops people from moving in one way or another. There is no cure. MS causes loss of coordination, memory, extreme fatigue, paralysis, blindness, and many other symptoms. These problems can be permanent or they can come and go.

More than 400,000 Americans have MS, and every hour someone is newly diagnosed. The National Multiple Sclerosis Society recommends treatment with one of the FDA approved disease modifying drugs to lessen the frequency and severity of attacks and to help slow the progression of disability. Unfortunately, the cost is often financially devastating. I know this personally.

Four of the six FDA approved disease modifying drugs are considered biological drugs. They range from $16,000 to $25,000 a year. That is about twice the amount of Social Security disability I receive annually. For me, sometimes the financial struggle to get my treatment can be troubling, more troubling than this incurable disease.

I am here today to appeal to the committee. My personal story is an example of the immediate need for this legislation that Chairman Waxman has introduced.

In the past I have struggled a lot with my MS and with trying to get the prescriptions I need to feel a little better. I was diagnosed with MS in April 2000 at 37 years old. In August 2000, I was prescribed Avonex, a biological drug from Biogen. The cost of Avonex is high, and I did whatever I could to afford my prescribed therapy. I sold my computer, I disconnected my phone, I skipped paying a lot of my bills. Despite this, I lost my home before the end of 2001 and I was living in my car. From 2001 to 2005 I was homeless.

I struggled for years to get approval from Social Security and I tried for over 3 years to be approved for subsidized housing. I was even turned down for help at shelters because of my MS. The staff there felt that I was a health liability due to my problems with balance and frequent falls. I became accustomed to begging, borrowing, and pleading for any help so I could get treatment.

Unfortunately, access to my treatment was sporadic and I paid the consequences with increased symptoms and more frequent attacks. It was a terrible cycle. As a result of not having access to Avonex for an extended period of time in 2004 I was hospitalized. The cost of my 24 hour hospital stay was nearly $1,000. I am still trying to pay that bill.

Today, after finally being approved for Social Security disability, I receive $1,100 a month, and I am covered under Medicare. I have coverage for my medications, but my co-payment is $220 a month just for Avonex. When you only have $1,100 a month to live on, $220 might as well be $220 million.

I don't want to be homeless or live in my car again, so I cannot miss rent. I don't want to risk my health, so I cannot skip too many meals. I often skip paying bills, but I cannot get too far behind or risk losing my electricity or other vital services. And I do my best to pay my share to those who provide my treatments. Even today I must miss my treatments occasionally. There is simply nothing I can do sometimes.

It is a misconception that help is readily available. Existing programs are often difficult to navigate, have varying criteria, take a long time, and sometimes run out of money. For example, last year I was finally approved for assistance by the National Organization for Rare Disorders. Before I received my assistance they ran out of funding. It was also possible to get assistance sometimes from

Biogeniodec. After asking them for help over a year ago, I think I am close to getting help with coverage during the Medicare part D donut hole, which I will already enter in April. I learned my lesson, though. This time I know not to count my chickens before they hatch.

As a person with MS, I take other prescription drugs for hypertension, depression, and several supplements. The difference is that the generics are available. This keeps my co-payments low and manageable. Most importantly, I do not have to miss these treatments because I cannot afford them. But this is not true for my MS therapies and never will be unless something changes.

Hopefully you can help with a solution. I am a person with a chronic, life-long, costly disease, but I want to stay out of a wheelchair, I want to stay out of the hospital, I want to contribute my talents to the community, I want to pay my taxes, I want to be healthy so I am able to help others who have MS. I want to stay on my treatment. If I don't have access to treatments, my health will decline.

The stress from the story I have told you, which I live with, has caused me to begin to lose my hair. Frankly, I don't really care. I just want to battle this beast that is trying to take away my movement.

My story is not unique. Millions rely on biologic drugs. Millions struggle terribly with the cost. If I can leave this committee with one thought, it is that no matter how good a drug is supposed to be, it has no chance of being effective if it is not affordable to those who need it.

For a long time no treatments were available for MS. Now there are. The sad thing is it doesn't matter. Some people just can't afford them. The cost is too much. We have to change that. This legislation has the power to move us a little closer. We all know that providing more affordable medications for all Americans is a serious priority. For biologic MS therapies, we will never, ever reach that goal if we don't start by simply providing the pathway. It is a necessary first step.

Thank you again for your invitation and attention. I hope you remember me, and people like me, as you consider this legislation. Please help provide more affordable biological drugs for those who desperately need them. Help establish a regulatory pathway for the FDA to review and approve follow-on biological therapies.

Thank you.

Chairman WAXMAN. Thank you very much, Ms. Brown.

Ms. Nathan.

STATEMENT OF MARY NATHAN

Ms. NATHAN. Mr. Chairman and distinguished members of the committee, I want to thank you for the opportunity to testify before you today. My name is Mary Nathan, and I am affected by Gaucher disease.

As one of 4,800 people being treated worldwide with Cerezyem, I understand, in a very practical way, what it means to be alive because of a recombinant biological medicine. I also understand what happens when the cost of a life-saving drug is unaffordable.

Gaucher disease is a rare genetic disorder classified into three categories and characterized by the deficiency of an enzyme necessary to break down fats called glycolipids. Because the enzyme is in short supply, lipids collect in the spleen, liver, bone marrow, and other organs. Left unchecked, the accumulation of lipids causes problems such as anemia, bleeding, organ dysfunction, abdominal enlargement, deterioration of the joints and bones, breathing problems, fatigue, and reduced ability to fight common infections. Type I is the most common. It strikes 1 in 40,000 people in the general population, and 1 in 600 Jews of Eastern European origin.

When I was diagnosed in 1966 at the age of 11, very little was known about Gaucher disease. Given the increased size of my spleen and my low blood count, doctors scheduled me for a splenectomy within weeks of my diagnosis. Shortly after that I was hospitalized with a high fever, excruciating pain, and an inability to walk. We learned later that lipids had migrated quickly to my bones, since the doctors had removed my spleen. We also learned that I had experienced a Gaucher bone crisis, a painful episode that would repeat often as my disease progressed.

By the time I entered college there was little doubt that I had a severe form of what is known as Type I Gaucher disease. At the age of 23 I underwent orthopedic surgery to straighten my leg and replace my destroyed hip. After a long recovery I was able to walk without pain for the first time in years. This respite lasted until 1988, when the implanted prosthesis became painful and unstable, so again I underwent surgery and began to experience complications that left me fighting for my life.

My red blood cell count was dangerously low due to a reaction, depriving my bones of oxygen. I then began to experience an ongoing cascade of bone infarcts, vertebrae fractures, and a serious fracture of my other hip.

To head off further damage, my doctor suggested a surgery of last resort known as a girdlestone procedure to repair my hip. Few patients ever walk again after this procedure.

What happened next marked a historic medical breakthrough that would change the course of my life and my disease. After 30 years of intensive scientific research, scientists at the National Institutes of Health discovered a treatment for Gaucher disease, and in April 1991, the Food and Drug Administration approved a commercial version called Ceredase.

After 3 years of enzyme replacement therapy, my overall health improved to a point where reconstructive hip surgery was possible. In November 1994, after 7 years in a wheelchair, I took my first real steps.

There is no question in my mind that I am alive today because of the orphan drug Ceredase. What concerns many of us, however, is that the miracle drug is priced out of the reach of individuals, and thus poses unprecedented challenges for patients who need the drug, for the doctors who treat us, for employers struggling with the high cost of health insurance, and for insurers and government programs helping to pay our medical bills.

In 1994 most patients were converted to Cerezyme, the Genzyme Corp.'s newly approved orphan drug, to replace Ceredase. The cost of Cerezyme differs from patient to patient because dosages are

based on body weight. My dosing regimen is 60 units per kilogram of body weight for infusion. At 130 pounds, my treatment runs about $12,600 per administration, or about $300,000 a year for 24 doses. An additional $25,000 in cost is added for administering the drug and testing and monitoring my response and overall health. This brings the cost for all charges related to my treatment to over $328,000 a year. Now, over a 16-year period since its approval in 1991, I estimate that the payments for my drug have reached well over $4.5 million.

In conclusion, the wave of the future in medicine is biotechnology to treat rare diseases like mine and those diseases affecting wider populations. There is no reason why biogenerics cannot take their rightful place in America's marketplace alongside generic drugs.

Based on some estimates, it is said that biogenerics could save between 10 percent and 20 percent. If that holds true, millions of dollars could be saved annually just for the 4,800 patients currently on Cerezyme.

Mr. Chairman, I want to thank you personally for introducing your legislation. It is time to make safe and effective life-saving biotech therapies accessible and affordable to the millions who need them.

The Access to Life-Saving Medicines Act will create competition in the marketplace and, in turn, foster innovation. Hopefully a balance will be struck that encourages innovation yet allows more affordable follow-on biologics to come to the marketplace.

Thank you for your time and attention to my testimony.

[The prepared statement of Ms. Nathan follows:]

Testimony of Mary Nathan

before the

U.S. House of Representatives

Committee on Oversight and Government Reform

"Access to Life-saving Medicines Act of 2007"

Monday, March 26, 2007

Mr. Chairman and distinguished members of the Committee, I want to thank you for the opportunity to testify before you today. My name is Mary Nathan and I am affected by Gaucher Disease.

As one of the 4,800 people being treated worldwide with Cerezyme®, I understand, in a very practical way what it means to be alive because of a recombinant biologic medicine. I also understand what happens when the cost of a life-saving drug is unaffordable.

What is Gaucher Disease?

Gaucher disease is a rare genetic disorder characterized by the deficiency of an enzyme necessary to break down fats called glycolipids. Because the enzyme is in short supply, lipids collect in the spleen, liver, bone marrow, and other organs. Left uncheck the accumulation of lipids causes problems such as anemia and bleeding, organ dysfunction and abdominal enlargement, deterioration of the joints and bones, breathing problems, fatigue, and a reduced ability to fight common infections.

Gaucher disease is classified into three categories - Types I, II and III. Type I, the adult form, is usually the least severe and is also the most common. Occurring among all racial and ethnic groups, this condition affects an estimated 20,000 Americans. It strikes one in 40,000 of the general population, and one in 600 Jews of Eastern European heritage.

The disease differs significantly from person to person. Some are asymptomatic or have minimal symptoms, while others experience severe and chronic problems causing life-long disability.

My Journey with Gaucher Disease

Gaucher disease has been my constant companion since my diagnosis in 1966 at the age of eleven. Very little was known about the disease at the time, and treating physicians mostly had to guess what was happening to me and what course of treatment to pursue.

Given the increased size of my spleen and my low blood count, doctors scheduled me for a splenectomy within weeks of my diagnosis. I bounced back from the operation. In fact, I was doing so well that I was able to attend an international children's camp in Denmark.

That wonderful adventure came to an abrupt end when I was hospitalized in Denmark with a high fever, excruciating pain and an inability to walk. I was immediately flown home in a stretcher and met in New York by my worried parents. We were to learn later that lipids had migrated quickly to my bones since doctors had removed the one place where they are most likely to collect – the spleen. We also learned that I had experienced a Gaucher bone crisis, a painful episode that would be repeated often as the disease progressed.

By the time I entered college, there was little doubt that I had a severe form of Type I Gaucher Disease. My blood count remained low and I had difficulty walking due to a curvature of my leg bone and a deteriorating hip joint. Through all the pain and discomfort, I eventually graduated, found a job and got my own health insurance.

At the age of 23, I underwent orthopedic surgery to straighten my leg and replace my destroyed hip joint. After a long recovery, I was able to walk without pain for the first time in many years. In better health, I started graduate school and focused on my career.

This respite lasted until 1988 when the prosthesis implanted when I was 23 became painful and unstable. Again, I underwent surgery. Fortunately, I was able to arrange time off from my demanding job as executive director of a professional association.

Unlike previous surgeries, this time I began to experience complications that left me fighting for my life. The Gaucher-related problems escalated rapidly, requiring hospitalization for the better part of a year. My red blood cell count was dangerously low, depriving my bones of oxygen. I then began to experience an ongoing cascade of bone infarcts, vertebrae fractures, and a serious fracture of my other hip.

To head off further damage, my surgeon decided on a simple surgery to repair my other hip. Known as a girdlestone procedure, it is a surgery of last resort. Few patients ever walk again.

Still seriously ill and confined to a wheelchair, I was discharged from the hospital. Physically and mentally exhausted and terrified of living in a wheelchair, I was financially ruined and out of a job. I now faced a life completely dependent on family and friends, not knowing what to expect or how to cope with the devastation of my disease.

Breakthrough Therapy Discovered

I turned to family and friends for help and within a few months, I was living in Massachusetts with a friend. This arrangement worked well because I could consult with the Gaucher Disease specialists at Massachusetts General Hospital. They provided the first glimmer of hope by suggesting that my hip problems might be corrected if my blood picture and stamina improved.

What happened next marked an historic medical discovery that would change the course of my disease. After 30 years of intense research, scientists at the National Institutes of Health developed a treatment for Gaucher Disease, and in April 1991, the Food and Drug Administration approved a commercial version Ceredase®. The enzyme my body could not produce could now be found in a vial.

Treatment with Ceredase® began shortly after approval. I saw a dramatic improvement during the first year. As treatment continued, my blood count returned to normal and the size of my liver decreased. Even the level of pain seemed better and the bone flare-ups vanished.

After three years of enzyme replacement therapy, my overall health improved to the point where reconstructive hip surgery was possible. The remarkable surgery that gave me a new right hip was complicated and painful, but I did make slow, steady progress. On my fortieth birthday in November 1994, after seven years in a wheelchair, I took my first real steps. As the months passed, I was able to walk further distances and before long I could walk unaided.

Cost of Care

There is no question in my mind that I am alive today because of the development and commercialization of the orphan drug Ceredase®. Others with Gaucher Disease have similar stories and, like me, are grateful to the Genzyme Corporation for bringing Ceredase® to market.

What concerns many of us, however, is that the miracle drug is priced out of the reach of individuals and thus poses unprecedented challenges for patients who need the drug, the doctors who treat us, for employers struggling with the high cost of health insurance, and for insurers and government programs helping to pay our medical bills.

The Genzyme Corporation sold its flagship product Ceredase® from 1991 to 1994 when most patients were converted to Cerezyme®, the company's newly approved orphan drug made in genetically engineered cells rather than from purified human placentas.

The cost of Cerezyme differs from patient to patient because dosages are based on body weight. My dosing regimen is 60 units per kilogram of body weight per infusion. At 130 pounds, my treatment runs about $12,643 per administration or about $303,432 a year for 24 doses.

In my case, the cost of administering the drug is another $10,000 a year, while related expenses for testing and monitoring my response to the drug and overall health are $15,000 annually.

This brings the cost for all charges related to my treatment to $328,432 a year. Over a sixteen year period, I estimate that the payments for my drug have reached well over $4.5 million.

Health Insurance Issues

Gaucher patients struggle to get and maintain sufficient health insurance to cover their medical bills. This task is made even more difficult because of business policies and common trends found throughout the health insurance industry. Pre-existing disease can present formidable barriers to those seeking insurance. Some insurance companies permanently exclude specific conditions while others set a waiting period of several months to a year. Many patients, including myself, purchase an individual policy while covered by other insurance. This allows full coverage until the waiting period ends.

The insurance practice of placing a dollar limit or "cap" on lifetime benefits is a cause of great anxiety among Gaucher patients. While many patients and their families have good coverage, others have already exceeded their million dollar limits. In these instances, patients try to purchase a new policy and are often assisted by reimbursement specialists at the Genzyme Corporation.

Conclusion

Mr. Waxman, I want to thank you for introducing the "Access to Life-Saving Medicines Act." It is time to make lifesaving biotech therapies accessible and affordable to the millions who need them. There is no reason why biogenerics can not take their rightful place in America's marketplace along side generic drugs.

The wave of the future in medicine is biotechnology-derived products and devices to treat rare diseases like mine, and those diseases affecting wider populations. But the question is, "Can the healthcare system withstand the costs associated with these miracle drugs?" I personally do not feel that it can.

I read recently that your legislation could initially save the American people about 10 percent to 20 percent over existing biotech therapies. For me, that would be a savings of between $30,343 and $60,686 annually. If you do the math for the 4,800 patients currently on Cerezyme®, just based on the cost of my treatments and my body weight, the healthcare system could save between $145 million and $291 million annually.

Mr. Chairman, patients like me need and want safe and effective medicines that they can afford.

Today there are over 300 orphan drugs treating well over 14 million people across the United States. Twenty-one percent of those are biologics. But there are millions more waiting on the sidelines hoping against hope that one day they, too, will have a drug or biologic to treat their disease. The "Access to Life-Saving Medicines Act" will create competition in the marketplace and, in turn, foster innovation.

A balance must be struck that encourages innovation, yet allows more affordable follow-on biologics to come to the marketplace. Hopefully, in years to come, there will be many more than 300 orphan products available to patients.

Thank you.

Chairman WAXMAN. Thank you very much, Ms. Nathan.

Ms. Barnett.

Ms. NATHAN. You are welcome.

STATEMENT OF NELDA BARNETT

Ms. BARNETT. Mr. Chairman and members of the committee, I am Nelda Barnett of AARP's Board of Directors. AARP appreciates the opportunity to testify in support of creating a pathway for generic biologics.

AARP has endorsed the Access to Life-Saving Medicine Act because we believe this legislation will enable the FDA to establish a process for the approval of safe, comparable, and interchangeable versions of biologics. We call on Congress to pass the legislation this year.

Biologics are used every day to treat serious diseases such as cancer, multiple sclerosis, anemia, and rheumatoid arthritis. While biologics hold great promise for treating some of the most serious diseases, these treatments can be expensive, costing tens and hundreds of thousands of dollars. Some people are fortunate enough to have insurance coverage or the means to be able to afford these medications, but many are not so lucky.

Nothing illustrates how important it is that we have a pathway to lower-cost generic versions than the stories of millions of Americans who currently cannot afford high-priced biologic drugs, such as we have just heard.

My colleague on AARP's board of directors, Bonnie Cramer, could not be here today, but she has asked that I share with you one particular story. Bonnie suffers from severe rheumatoid arthritis, and over the years 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 medication. One particular woman was so affected by the disease that her fingers were gnarled and she had difficulty walking and used all of her energy just to get through the 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. She says, "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 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 lives significantly?"

The astronomical cost of these drugs not only impacts consumers, but also health care payers such as employers, private health care plans, public programs such as Medicare and Medicaid. One way to control these costs is to provide a pathway for the approval of generic versions of these drugs. Any prescription drug therapy treatment must be affordable and safe in order to be effective for individuals. H.R. 1038 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 the brand name biologics, surely has the ability to provide a pathway for generic approval of the same biologic.

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. H.R. 1038 provides FDA the authority to produce the safe, comparable, or interchangeable version of the biologic. Our members and all Americans need Congress to enact this bipartisan 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.

Thank you again for inviting us here. I am happy to answer any questions.

[The prepared statement of Ms. Barnett follows:]

TESTIMONY BEFORE THE

HOUSE COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

ON

SAFE AND AFFORDABLE BIOTECH DRUGS—THE NEED FOR A GENERIC PATHWAY

March 26, 2006

WASHINGTON, D. C.

WITNESS: NELDA BARNETT
AARP BOARD MEMBER

For further information, contact:
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Mr. Chairman and members of the Committee, I am Nelda Barnett, a member of AARP's Board of Directors. AARP appreciates the opportunity to testify today in support of creating a pathway for generic biologics. 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). The Hatch-Waxman Act of 1984 created a pathway for the Food and Drug Administration (FDA) to approve generic versions of traditional prescription drugs. Currently, there exists no similar process at the FDA for the approval of generic biological products.

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.

One woman's story

Nothing illustrates how important it is that we have a pathway to lower cost generic versions than the stories of those Americans who currently cannot afford high priced biologic drugs.

One of my colleagues on AARP's Board of Directors has asked that I share with you her particular story. Bonnie suffers from severe rheumatoid arthritis and, over the years, has undergone a variety of treatment options. Like any patient she researched her disease and had extensive conversations with her doctor

about possible treatment options. Her research led her to the biologic drug, Enbrel. Because all other forms of treatment had failed, she was fortunate to have her insurance cover this biologic drug.

Shortly after beginning to take the biologic, Bonnie had no sign of the disease and was able to work and enjoy life in a way she had not done for over 30 years. Having access to this drug has made a miraculous difference in Bonnie's health and well-being. But not everyone has been so lucky. Bonnie has encountered many people who suffer from the same condition who are not able to afford the biologic medication. One particular woman was so affected by the disease that her fingers were gnarled, she had difficulty walking, and like many who suffer from chronic illness, 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. Like Bonnie, she had gone through every possible treatment option, but unfortunately wasn't getting any better – and in fact was getting worse. She had read about this new drug, but there was no way that she could afford 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. You watch, in disbelief, as you grow more and more physically incapacitated day by day. I know what hope biologics can give to someone whose whole life is affected. I know how it can affect a person's life. 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 lives significantly?"

Con umers n ed access to safe and eff ctive g n ric biologic .

Use of biologic drugs is increasing every year[1] to treat diseases and conditions such as cancer, multiple sclerosis, anemia, and rheumatoid arthritis. Research and development into this vital field is growing – there are currently hundreds of applications in the pipeline. These treatment therapies are, in many cases, truly cutting edge technology. For someone like Bonnie who has rheumatoid arthritis, her biologic treatment therapy made 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 as much as $10,000 per year. 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.[2] Similarly, a person diagnosed with colon cancer may be prescribed Avastin, which can cost $100,000 per year, more than the average cost of a four-year college education.[3]

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, spending on biologic drugs continues to

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[1] 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).
[2] 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).
[3] 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).

outpace even that of traditional brand name prescription drugs,[4] whose cost increases – at twice the level of inflation – are also too high.[5] One way to control these costs is to provide a pathway for the approval of generic versions of these products. A recent study by a large pharmacy benefit manager estimated a savings of $71 billion over ten years to the entire health care system if the FDA approved a pathway for generic biologics in just four therapeutic areas: interferons for multiple sclerosis; erythropoietin for anemia; growth hormone for growth failure; and insulin for diabetes.[6]

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.[7] Approximately 56 percent of all prescriptions filled in the U.S. – more than one billion prescriptions every year – are lower-cost generic prescription drugs.[8]

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

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[4] Elise Wang, et. al, A Global "Generic Biologics" Guidebook, Citigroup, Nov. 6, 2006, pg. 30.
[5] David J. Gross, Leigh Gross Purvis, and Stephen W. Schondelmeyer, *Trends in Manufacturer Prices of Brand Name Prescription Drugs Used by Older Americans, 2006 Year-End Update*, AARP Public Policy Institute Data Digest #DD154 (Washington, DC: AARP), March 2007 (finding that on average, pharmaceutical manufacturer prices for the 193 brand name drugs most widely used by older Americans rose at nearly twice the rate of general inflation in 2006).
[6] Express Scripts, Financial Impact of Biogenerics, March 16, 2007.
[7] CBO, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.
[8] Statistics from the Generic Pharmaceutical Association (Available online at: http://www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm).

drugs. And the pharmaceutical industry – now the fifth most profitable industry in the country[9] – has been hugely profitable.

Legislation ensures safety and access.

Any prescription drug treatment therapy regimen must be affordable and safe in order to be effective for individuals. Generic versions of biologics will produce lower cost alternative treatment therapies, but these treatment therapies must also be safe in order to be effective.

While biologics are more complex than traditional prescription drugs, complexity alone is not a valid reason to prevent research 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 does not mandate that the FDA approve a certain number of applications – only that FDA provide for the 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.

As science advances, we can expect prescription drugs to become an increasingly important component of health care, and for biologic drugs to become a larger component of drug spending. When brand name prescription drugs go off patent, a generic manufacturer can begin marketing its lower cost

[9] Fortune 500 2006, "Most Profitable Industries: Return on Revenue," April 17, 2006.

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.

It is critical not only for individuals, but for all health payers – including federal and state governments, employers and insurers – that we begin to take steps to lower the cost of these biologics. 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.

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.

Chairman WAXMAN. Thank you very much, Ms. Barnett.

Ms. Mathur.

STATEMENT OF PRIYA MATHUR

Ms. MATHUR. Good afternoon. Mr. Chairman and members of the committee, I commend you for convening today's hearing and for the introduction of bipartisan legislation to enable consumer participation in the biopharmaceutical marketplace.

On behalf of the California Public Employees' Retirement System [CalPERS], I welcome the opportunity to testify about this issue of importance to our members, to our State, and to our Nation.

Let me begin by introducing myself and CalPERS. My name is Priya Mathur, and I was elected by 400,000 public sector employees to serve on the board of CalPERS, to invest their $230 billion of retirement assets, and to manage their multi-billion-dollar health care program.

CalPERS' health program covers 1.2 million active and retired public employees and their families. Notably, CalPERS is the third-largest purchaser of employee benefits in the Nation, behind only the Federal Government and General Motors, and it 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 members' prescription drugs. 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, the high cost of biopharmaceutical products presents an unsustainable challenge to calPERS and to our entire health care system.

CalPERS has long been a leader in implementing cost effective health care programs. Among many strategies, we have instituted innovative prescription drug benefit cost-sharing designs to maximize the use of generics and therapeutically appropriate brand name drugs. CalPERS has actually achieved tremendous success in controlling prescription drug costs through the use of generics. This has been possible thanks to the chairman, whose efforts two decades ago led to the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984, what we call Waxman-Hatch.

As you well know, Waxman-Hatch gave the FDA the authority to provide an abbreviated approval process for those products deemed equivalent to an innovator product after patent expiration. Without generic substitution, we estimate that our costs would be about 60 percent higher than they are today. Generics save our enrollees and our State taxpayers hundreds of millions of dollars every year.

In spite of all of our cost containment efforts, CalPERS has seen an average annual increase of about 13.5 percent for our HMO and PPO products since 2002.

Mr. Chairman, CalPERS' spending for biotech products is distressingly substantial and rising at a rate that is significantly higher than traditional pharmaceuticals. 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 the specialty drug category.

Total spending for specialty drugs was $83.7 million in 2006, a 1-year increase of 16.9 percent, 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.

CalPERS supports a competitive health care marketplace that leads to innovation and life-saving medicines; however, competition does not exist today because the FDA asserts that it does not have the authority to approve biogeneric products. As a result, today's biotech companies are benefiting long after patents expire and are profiting at the expense of all Americans.

CalPERS supports giving the FDA explicit authority to approve biogeneric products that are safe. Without the ability to access less-expensive comparable and interchangeable biopharmaceuticals, CalPERS ultimately will be forced to raise prescription drug co-pays or raise premiums, shifting the increasingly unaffordable costs onto the individuals who can least afford them.

Mr. Chairman, before I conclude I need to address one important issue. The opponents of this legislation—as you point out, they are limited to the biotech industry—are claiming that those who support your legislation are ignoring the safety threat of bringing biogenerics to the marketplace. I want to be perfectly clear. The safety and health of our members comes first in any decision we make on any health care policy. Therefore, we strongly support providing FDA with full discretion to make the ultimate decision about whether and when any prescription drug product, be it brand name or generic, comes to market. Your legislation does just that.

Mr. Chairman, CalPERS is proud to add our support to the growing and diverse list of stakeholders who support your legislation to open the door to biogeneric competition. Thank you for giving us this opportunity.

I would be happy to answer any questions.

[The prepared statement of Ms. Mathur follows:]

Testimony by Priya Mathur
Vice Chair, Health Benefits - Board of Administration
California Public Employees' Retirement System

Committee on Government Oversight and Reform
House of Representatives
U.S. Congress

March 26, 2007

Mr. Chairman, Mr. Davis and members of the Committee. Thank you for providing California Public Employees Retirement System (CalPERS) with the opportunity to testify on the high cost of biopharmaceuticals and the need to establish a safe pathway for the approval of biogenerics. I am Priya Mathur. 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 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.

Mr. Chairman, I commend you for convening today's hearing and for the introduction of bipartisan legislation to introduce competition into the biopharmaceutical marketplace. On behalf of CalPERS I welcome the opportunity to testify about this issue of importance to our members, to our state and to our nation. I would also like to thank the eleven cosponsors of your bill –

Representatives Emerson, Palone, Emanuel, Hirono, Stark, Kilpatrick, Conyers, Abercrombie, Wamp, Grijalva, and Pastor – for their leadership on this pressing issue.

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.

Today 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 represents 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 medications and mail-order, particularly for the treatment of chronic diseases.

CalPERS has actually enjoyed tremendous success in controlling prescription drug costs through the use of generics. This has been possible, thanks to the Chairman, whose efforts two decades ago led to the enactment of the "Drug Price Competition and Patent Term Restoration Act of 1984," what we call Waxman-Hatch.

As you well know, Waxman-Hatch 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

Mr. Chairman, 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 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 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.

Mr. Chairman, before I conclude I need to address one important issue. The opponents of this legislation – and as you point out, they are limited to the biotech industry – are claiming that those who support your legislation 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. Your legislation does just that.

Mr. Chairman, 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 your legislation to open the door to biogeneric competition. We stand ready to work with you to complete the work you started in Waxman-Hatch by making biogenerics a safe and affordable alternative for consumers. Thank you for giving us this opportunity to share our thoughts on this life-impacting issue. I'd be happy to take any questions that you or other members of the Committee may have.

Chairman WAXMAN. Thank you very much for your testimony.

We are going to ask questions after everybody is finished.

Mr. McKibbin.

STATEMENT OF SCOTT MCKIBBIN

Mr. MCKIBBIN. Thank you, Mr. Chairman, and thank you for the opportunity to speak on behalf of Illinois Governor Rod R. Blagojevich in support of establishing a pathway for generic biopharmaceuticals.

I want to applaud Chairman Waxman for his vision, recognizing that escalating cost 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 in the Nation as a whole.

Further, I would like to recognize Illinois Congressman Emmanuel for his cosponsorship of H.R. 1038, the Access to Life-Savings Medicine Act, and for supporting these important measures.

In my present role as a Special Advocate for Prescription Drugs, I have functional accountability for overseeing prescription drug spending for the State of Illinois. I am also a two-time kidney cancer survivor, and can speak personally from experience on both the value and the cost of therapies that treat such dreaded diseases as cancer.

I want to make it clear that I have a dual role as Special Advocate. The State of Illinois, as every State, has a responsibility to ensure that prescription drug 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 generic legislation.

While some in this debate are seeking to obscure the real issue 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.

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 health care costs to bankrupt our State or to negatively impact employers or the overall business climate of our State. To this end, Governor Blagojevich has introduced a comprehensive program to expand 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 health care costs covered under the existing insurance plans.

There is some debate as to whether the annual increase of the cost of biopharmaceuticals is 15, 17, or 20 percent, but the difference is, in fact, not material. If, as I believe and my data will show, these expenditures for products are rising at an average of slightly larger than 15 percent annually, then within 5 years what Illinois spends on these drugs today will double. That would have

a dramatic negative effect. We would not be able to afford these medications.

Many States probably don't realize the depth of what they are spending now on biopharmaceuticals. According to IMS, biopharmaceutical sales in 2006 grew to $40.3 billion. While the spending has escalated, a debate over potential for generic biopharmaceuticals has spanned four FDA Commissioners, all with a variety 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 and impact of spending on biopharmaceuticals for Illinois, we examined the leading products and what the State of Illinois spends on these products. The results were staggering.

For our 227,500 member employee retiree group, the State of Illinois spent $33.2 million on a select list of approximately 100 biopharmaceuticals during the fiscal year that just ended July 2006. With that trend, this represents over 12 percent of our entire cost for drugs, and is growing at an astronomical rate both on the price and the utilization side of the ledger. The ingredient cost increase was 49.9 percent, and the plan cost per member was 50.3 percent.

The number of prescriptions for this select list of biopharmaceuticals also rose significantly, a nearly 29 percent increase. For programs administered under the State Medicaid Agency, we 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 $1,662,000, paid for under the pharmacy benefit side, and an estimated $75 million paid for under the medical and the Part D wrap-around program. The grand total exceeded $200 million a year, without trend.

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 be only 10 or 20 percent. But let's look at the worst case scenario, a 10 percent savings. If Illinois was able to reduce its 15 percent, 16 percent annual increase in spending on biopharmaceuticals by even 10 percent, 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.

The other issue to consider about savings is this—it appears an obvious one from my perspective, but seems lost in this 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 even higher expenditures associated with those biopharmaceuticals. Every day that we delay in creating a pathway for generic competition is a day of potential lost cost savings to States, to taxpayers, and to consumers. We can not afford to wait any longer to begin the savings, even if, as opponents predict, the savings would initially only be modest.

Chairman WAXMAN. Thank you very much, Mr. McKibbin. Are you just about to conclude?

Mr. MCKIBBIN. I have just a few more words, Mr. Chairman.

Chairman WAXMAN. OK.

Mr. MCKIBBIN. I appreciate it.

I would just like to urge Congress to approve this legislation to authorize the FDA to apply sound scientific regulatory criteria that would give Illinois and other States and every consumer and taxpayer lower biopharmaceutical products and increased access, the result from the cost savings.

Thank you, Mr. Chairman.

[The prepared statement of Mr. McKibbin follows:]

Testimony of Scott McKibbin
Special Advocate for Prescription Drugs
State of Illinois

Testimony Before the House Committee on Oversight and Government Reform

On the Subject of Approval Pathway for Generic Biopharmaceuticals

March 26, 2007

Thank you for the opportunity to speak on behalf of Illinois Governor Rod R. Blagojevich in support of establishing a pathway for generic biopharmaceuticals. I want to applaud Chairman Waxman 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 access to life-saving biopharmaceuticals both in Illinois and the nation as a whole. Further, I would like to recognize Illinois Congressman Emanuel for his co-sponsorship of H.R. 1038, the Access to Life-Saving Medicine Act, and for supporting these important measures.

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). 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 in 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 one that negatively impacts 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 per member was 50.3%.

The number of prescriptions for this select list of biopharmaceuticals also rose significantly, a nearly 29% increase.

For 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 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, a patient 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; a patient 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, a patient 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.

Chairman WAXMAN. Thank you very much for your testimony.

Dr. Grabowski.

STATEMENT OF HENRY GRABOWSKI

Mr. GRABOWSKI. Thank you, Mr. Chairman and members of the committee. I am Henry Grabowski, professor of economics at Duke University.

My comments will focus on the differences between generic drugs and follow-on biologics and how these differences affect the expected budgetary savings. I also will discuss the importance of data exclusivity for innovation incentives. With my colleagues, I have examined these issues in two recent peer reviewed studies. I will make these studies available for the record, along with my statement.

Based on our analysis, we conclude that the cost of entry will be significantly higher for follow-on biologics than generic drugs. We expect fewer firms will enter, and average prices will decline less for follow-on biologics. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the Government and to other payers.

Second, in designing a pathway for follow-on biologics it is also very important that Congress balance price competition and innovation incentives. In this regard, it is important to include in the legislation a data exclusivity period that takes account of the high cost and risk of developing new entities. My statement provides data from a new study that is peer reviewed and co-authored with Joe DiMasi in this regard. The cost of R&D for a representative new biologic is now over $1 billion when one takes account of preclinical and clinical expenditures, the cost of failures, the cost of capital, and process engineering, which is higher for biologics than pharmaceuticals.

So let me now briefly summarize some of the key differences between follow-on biologics and pharmaceuticals that will affect cost savings in scoring procedures.

The first is clinical trial cost. As we have heard earlier today, some clinical trial data is going to be necessary to demonstrate comparable safety and efficacy, at least for the foreseeable future. In the case of European filings, the estimates range from $10 to $40 million for preclinical studies. This contrasts with $1 to $2 million costs for bioequivalents for generic drugs.

Second is development times. Estimates from generic firms indicate development times for a follow-on biologic are likely to range from five to 8 years. By comparison, generic drugs seldom require more than a few years to do required tests and gain regulatory approval.

Third is manufacturing cost and risk. The required capital investment in property, plant, and equipment and the cost of manufacture are also likely to be significantly higher for follow-on biologics.

Fourth, there are important differences on the demand side. It is unlikely that most follow-on drugs will be designated as interchangeable by the FDA, at least not for the foreseeable future and without extensive clinical trials. As a result, we expect the physicians will initially be cautious with respect to the substitution of

follow-on products. Health care providers and patients are likely to be wary until clinical experience has accumulated and shown that a follow-on product is a satisfactory therapeutic alternative to the original innovator products.

These costs and demand side differences have important implications for entry and price competition. In our research, we find the number of entrants and the priced discounts of a follow-on biologic are highly sensitive to fixed cost. As a consequence, even very large-selling biologics are likely to have only a few entrants. For markets with only one to three entrants, we project price discounts will be in the range of 10 to 25 percent. This is in accordance with European experience to date.

These differences also have important implications for scoring cost savings. In particular, cost saving estimates based on the experiences of generic drug utilization and pricing are subject to strong upward biases. A correct accounting of this and all other relevant factors would substantially lower the savings estimates in studies such as that by Express Scripts and the PCMA.

A recent analysis by Avalier Health has very different assumptions in some important dimensions, find much lower cost savings.

The remainder of my statement covers R&D costs and innovation incentives. I understand the bills under consideration have no data exclusivity provisions or patent restoration features for innovators. The fact that there is no data exclusivity provision would allow generic firms to challenge innovators' patents from the date of first marketing approval and to enter the market soon thereafter. The resulting uncertainty in IP litigation would have significant negative incentive effects on capital market decisions for private and public biotech firms with pipelines. Many of these firms are entrepreneurial in nature and have few if any profitable products.

The exclusivity period for pharmaceuticals under Hatch-Waxman is 5 years. R&D costs have increased substantially since Hatch-Waxman was enacted 20 years ago. Five years does not provide enough time for firms to recoup the high cost of discovering and developing a new medicine. Break-even returns on R&D for the average new drug and biological product now exceed more than a decade.

Since this legislation will essentially define the terms of competition between innovators and imitators for decades to come, it is critical that it maintains strong incentives for R&D investment in new biopharmaceuticals, as well as provide incentives for price competition.

A data exclusivity period of at least 10 years in length would recognize the high cost and risk of developing new biological entities and deter patent challengers from occurring and entering until a more mature phase of the product life cycle. This would also preserve incentives for the development of new indications for existing drugs and harmonize U.S. law with that of the European Union.

Thank you.

[The prepared statement of Mr. Grabowski follows:]

Statement
Henry G. Grabowski, Ph.D.
Duke University

House Oversight and Government Reform Committee
March 26, 2007

My comments will focus on how the market for follow-on biologics can be expected to evolve economically. Assuming a regulatory pathway is created by Congress, it is relevant to ask whether the economic impact will be the same as for generic drugs under Hatch-Waxman.

Biologics are typically more complex molecules than chemical drugs, and are not manufactured through chemical synthesis, but instead produced through biological processes involving manipulation of genetic material and large-scale cultures of living mammalian, microbial, or yeast cells. Biologics made in different cell lines or manufacturing plants might behave differently as medicines and exhibit unexpected adverse events *in vivo*. These fundamental differences between biological and chemical entities result in important differences in the economics conditions for follow-on biologics compared to generic drugs.

With a group of my colleagues, I have examined the differences between follow-on biologics and generic drugs from an economic perspective in two recent peer-reviewed studies. The first article, entitled "The Market for Follow-On

Biologicals," co-authored by Iain Cockburn and Genia Long, was published in the September/October 2006 issue of *Health Affairs*. The second paper, entitled, "Entry and Competition in Generic Biologics," is in press for a forthcoming issue of *Managerial and Decision Economics*.

Based on our analyses, we conclude that the costs of entry will be significantly higher for follow-on biologics than generic drugs. As a consequence, we expect fewer firms will enter, and average prices will decline less than for follow-on biologics than generic drugs. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the government programs and other payors.

In designing a pathway for follow-on biologics, it is also very important that Congress balance price competition and innovation incentives. The process for discovering a new biologic is lengthy, costly and risky. Over the coming decade, biopharmaceutical innovation can provide major improvements in the duration and quality of human life. It is important to preserve the incentives for innovators through a data exclusivity period that takes into account the high costs and risks of developing new biological entities.

DIFFERENCES BETWEEN FOLLOW-ON BIOLOGICALS AND PHARMACEUTICALS

Clinical Trial Costs

Biologicals made with different cell lines or manufacturing facilities can exhibit significantly different efficacy and safety characteristics. If the U.S. follows a similar approach to Europe's, some clinical trial data demonstrating comparable efficacy and safety will be required for follow-on biologics on a case by case basis. New follow-on entrants may not have to repeat all the original sponsor's clinical steps or incur the costs associated with large patient phase III trials. However, even relatively small trials in biologics of several hundred patients are likely to generate development costs of tens of millions of dollars and take many years to complete. Furthermore, firms can expect to incur additional costs for immunogenicity tests and pharmacovigilance studies.

In the case of European approvals, some estimates from generic company presentations and interviews suggest a plausible range could be $10 to $40 million for pre-market clinical studies. The exact amount is likely to depend on how well-characterized the molecule is and other scientific and technological factors. This contrasts with the $1 - $2 million cost necessary to demonstrate bioequivalence for generic drugs.

Development Times

Estimates from generic firms indicate that development times for a follow-on biological are likely to range from five to eight years. This estimate is based on one to two years for cell biology, one year for process analysis, two to four years for clinical trials, and one year for approval. By comparison, generic drugs seldom require more than a few years to do bioequivalence tests and gain regulatory approval.

Manufacturing Cost and Risks

The required capital investment in property, plant, and equipment, and the costs of manufacturing are also likely to be higher for follow-on biologics than for generic drugs. Cell culture facilities require significant capital and labor investment, taking on average three to five years to construct and costing $250 - $450 million. Plant investment must often be made before drugs enter clinical testing.

An alternative to manufacturing in-house is contract manufacturing. Contract manufacturing of follow-on biologics will be more costly than for pharmaceuticals, due to higher variable costs of production. Contract manufacturers also typically capture a share of the potential profit, limiting the amount ultimately passed on to end users. Due to increased demand associated with the large number of new biological

introductions, contract manufacturers have considerable leverage in negotiations with client firms.

Distribution Structure and Market Acceptance by Physicians

Biologic and drug markets also differ in the structures of their distribution systems and in the economic incentives for participants in the value chain. Most drugs are oral agents distributed through retail and mail order pharmacies. Generic drug products are designated as therapeutically equivalent and interchangeable by the FDA. Strong financial incentives and systems favor rapid generic penetration.

In contrast, biologics include both injected or transfused agents delivered in a physician's office, clinic, or hospital, as well as self-injectible products dispensed through pharmacies. It is unlikely that most follow-on biologics will be designated as interchangeable by the FDA. Instead, they will be treated as therapeutic alternatives by health care providers. Omnithrope fits this categorization, as does the initial human growth hormone products approved in Europe.

We expect that physicians will initially be cautious with respect to the substitution of follow-on products. Health care providers and patients are likely to be wary until clinical experience has accumulated and demonstrated that a follow-on product is a satisfactory therapeutic alternative to the

original product. The perspectives of specialist physicians and organized patient groups in therapeutic areas with high biologic usage will be important in driving or limiting demand for follow-on products.

To overcome barriers to physician and patient acceptance, follow-on biologic entrants may find it necessary to establish "reputation bonds" with branded products to capture and maintain market share. In this environment, market access is facilitated through specialist education and detailing, as well as through contracts with major managed care plans and coordination with centralized formulary policies. Relative to generic drugs, companies may have to incur the added costs of professional detailing forces, perhaps comparable to those of specialty pharmaceutical and biotechnology companies (estimated elsewhere at 40 people).

ENTRY AND PRICE COMPETITION FOR FOLLOW-ON BIOLOGICALS

In the case of generic drugs, a key economic driver of lower prices is the number of generic entrants. A recent analysis published in 2005 that I performed with Atanu Saha and colleagues, "Generic Competition in the U.S. Pharmaceutical Industry," quantifies the dynamic effects of generic entry. As more competitors enter, prices decline and the share of the molecule captured by generics increases. Our analysis indicates

that 10 to 20 generics are likely to enter for large selling products. In these cases, prices are typically driven down to marginal costs of production within a period of months. Large savings to payors and consumers can result when this intensive price competition occurs.

However, we expect the economic dynamics in the case of follow-on biologics will be different. This is due to the higher fixed costs for clinical trials, high manufacturing barriers to entry, and the slower penetration associated with the reluctance of physicians initially to switch patients to follow-on biological products. This will constrain the number of entrants in this market. Entry is the key economic driver of lower prices.

In my research study with David Ridley and Kevin Schulman, we find that the number of entrants and the price discounts of follow-on biologics are highly sensitive to fixed costs. As a consequence, even very large selling biological products are likely to have only a few entrants. Accordingly, price discounts are expected to be moderate. For markets with only one to three entrants, we project that price discounts will be in the range of 10 to 25%. This is in accordance with the European experience to date.

It is also important to remember that the current rapid pace of generic entry and penetration that now characterizes

most large drug products when patents expire took many years to evolve. We expect that this also will be true for follow-on biologics. A more robust follow-on industry will likely emerge as regulatory standards, process engineering, and demand evolve, but this will take many years, even for well-characterized biologics.

Implications for Cost Savings

Given the higher costs of firm entry and the likelihood of demand-side constraints and learning effects for follow-on biologics, cost savings estimates cannot be based on the experiences of generic drug utilization and pricing. Savings estimates based on these assumptions, like those from Express Scripts, are subject to strong upward biases.

A correct economic analysis must take account of the significant economic differences between generic drugs and biologics enumerated above. As discussed, our analysis predicts fewer entrants, smaller price discounts, and lower overall market penetration in the case of follow-on biologicals. A more conservative approach for estimating cost savings is therefore warranted, in our view.

A correct savings analysis must also take account of the time necessary to promulgate FDA regulations and review applications for follow-on biologicals. Even if legislation is

passed in 2007, several years are likely to elapse before a follow-on product is approved and launched in the United States.

A correct economic analysis must also recognize that the sales distribution of existing biotechnology is highly skewed, and that a significant percentage of the largest selling products are currently patent protected over the next decade. In a dynamic market like biopharmaceuticals, improved new products also will be introduced that will replace some of the market for the products subject to patent expiration.

A correct accounting of all these factors would substantially lower the savings estimates in the Express Script and PCMA studies. As a consequence, most of the projected savings in these studies are unlikely to be realized in the ten year scoring window. A recent analysis by Avalere Health, that has very different assumptions in some important dimensions, finds much lower cost savings.

R&D Costs of Innovators are Increasing

Joseph DiMasi and I recently examined the R&D costs and development times for a new data set of recombinant proteins and monoclonal antibodies. We found that mean out-of-pocket R&D costs to discover and develop a new biological entity (including the costs of failures) totaled $559 million. When capitalized to date of marketing at a cost of capital of 11.5%, R&D costs

increased to $1.24 billion. Compared to new chemical entities, we found new biological entities had higher preclinical expenditures and longer clinical development times, but also experienced higher probabilities of success. When adjusted for the time periods analyzed, we found that overall costs for new biological entities were comparable to new chemical entities. Both have been increasing much more rapidly than inflation in recent years.

We also found that the development of biologics entails higher manufacturing costs than new chemical entities. This reflects the need to resolve novel manufacturing challenges at the R&D stage for products developed through fermentation or fragile mammalian cell cultures. By contrast, manufacturing issues in R&D are more straightforward for new clinical drugs. Process specifications and know-how will be important for regulators to consider in developing guidelines for follow-on biologics, and raise important intellectual property issues.

INTELLECTUAL PROPERTY PROVISIONS AND DATA EXCLUSIVITY

Given the entrepreneurial character of the biotech industry, it is especially important that Congress carefully consider the intellectual property provisions that will govern competition between innovators and imitators. In particular, Congress will have to consider whether to award market

exclusivity to the first follow-on biological to successfully challenge a patent. Second, it will also need to decide whether to award innovators a data exclusivity period. This determines the earliest point in time that follow-on biologics can enter, based on an abbreviated process that relies in whole or part on innovators' safety and efficacy data.

Intellectual property has been an important factor for investment in the lengthy risk R&D process for new biological entities, and especially to biotech startups in securing venture funding and partnerships with larger firms. Product life cycles for new medicines span decades and R&D decisions are made with long time horizons on future returns. Legislators may view the encouragement of patent challenges and attendant litigation as a good short-term mechanism for exposing more biologics to follow-on price competition. But increased uncertainty and IP litigation in biotech also would have significant negative incentive effects on capital market decisions for developing private and public biotech firms with promising pipelines. Most of these firms have few, if any, profitable products.

The EU has recently instituted a ten-year data exclusivity period for new medicines of chemical or biological origin, with provisions for additional exclusivity for the approval of new indications. This prevents patent challengers from filing abbreviated follow-on applications until at least ten years have

elapsed. The comparable period for pharmaceuticals under Hatch-Waxman in the United States is five years. The patents of all commercially significant drug products are now challenged in a competitive race by generic firms to gain 180 day exclusivity.

R&D costs have increased substantially since Hatch-Waxman was enacted over 20 years ago. Five years does not provide enough time for firms to recoup the high costs of discovering and developing a new medicine. Breakeven returns on R&D for the average new drug products typically take more than a decade.

I understand that H.R.1038/S.623 have no provisions for data exclusivity for biological innovators. In effect, patents would be subject to challenge as soon as a new biological entity is approved by the FDA. A ten year exclusivity period, like that currently exists in Europe, would help balance innovation incentives and price competition when instituting a new regulatory pathway for biologicals.

A significant data exclusivity period is also important in terms of encouraging investment in new indications for approved biologics. New indications for approved medicines have led to important advances in several disease areas, including cancer and other life-threatening diseases. If a product is subject to patent challenges and follow-on entry very early in its product life cycle, then innovative firms will have much less economic

incentive to invest in the costly and risky process to gain approval for these new indications.

SUMMARY

It is hard to think of many activities that have the potential to increase human welfare more than new biological entities, from both a preventive and therapeutic standpoint. Over the coming decades, biopharmaceutical innovation can truly revolutionize health care and the treatment of many life-threatening and disabling diseases. But the resulting advances could also exacerbate budgetary pressures for Medicare and other payors. In establishing a new regulatory pathway for follow-on biologics, it will fall to Congress and the FDA to balance the objectives of innovation incentives, patient safety, and price competition as was the case when Congress created the Hatch-Waxman program more than two decades ago.

In crafting this legislation it is important that Congress recognizes the significant differences between generic drugs and follow-on biologicals that will affect how the market evolves from an economic perspective. Over the ten year budgetary scoring period, it is reasonable to expect modest cost savings, given the higher cost of entry and demand side constraints affecting follow-on biologics.

Since this legislation will essentially define the terms of competition between innovators and imitators for decades to come, it is critical that it maintain strong incentives for R&D investment in new biopharmaceutical medicines. A data exclusivity period of at least ten years in length would recognize the high costs and risks of developing new biological entities, and deter patent challenges from occurring until a more mature phase of the product life cycle. This would also preserve incentives for the development of new indications, and harmonize United States law with that of the European Union.

Entry and Competition in Generic Biologicals

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Abstract

By 2007 patents for several blockbuster biological products are expected to expire. The Food and Drug Administration is examining whether biologics can and should be treated like pharmaceuticals with regard to generics. In contrast with pharmaceuticals, which are manufactured through chemical synthesis, biologics are manufactured through fermentation, a process that is more variable and costly. Regulators might require extensive clinical testing of generic biologics to demonstrate equivalence to the branded product. The focus of the debate on generic biologics has been on legal and health concerns, but there are important economic implications. We combine a theoretical model of generic biologics with regression estimates from generic pharmaceuticals to estimate market entry and prices in the generic biologic market. We find that generic biologics will have high fixed costs from clinical testing and from manufacturing, so there will be less entry than would be expected for generic pharmaceuticals. With fewer generic competitors, generic biologics will be relatively close in price to branded biologics. Policy makers should be prudent in estimating financial benefits of generic biologics for consumers and payers. We also examine possible government strategies to promote generic competition.

1. Introduction

The Food and Drug Administration (FDA) is examining whether biological products can and should be treated like pharmaceuticals with regard to generics. The focus of the debate on generic biologics[1] has been on legal and health concerns, but there are important economic questions. How will differences in development and manufacturing costs and associated regulations affect the market for generic biologics? Will generic biologics be as competitive and provide the substantial financial savings provided by generic pharmaceuticals? We analyze market entry and prices in the generic biologic market using a theoretical model of generic biologics and regression estimates from generic pharmaceuticals.

There have not yet been any major market approvals of generic biologics due to three barriers. First, the biotechnology industry is young, so few patents have expired for major biologic products. Second, the regulatory framework for generic biologics has not been settled. Third, biologic products are complex and have high costs of establishing scientific and manufacturing capabilities (Humphreys 2004).

The first two barriers might fall soon. First, by 2007 patent expirations are expected for blockbuster biologics such as Procrit, Epogen, and Intron A (Humphreys 2004). Second,

[1] Throughout the paper we refer to "generic biologics" for the sake of symmetry with generic pharmaceuticals. The term "follow-on biologic" might be more appropriate than "generic biologic," given that the product might be required to complete clinical trials to demonstrate similar safety and efficacy to the originator.

FDA is considering guidelines for the approval of generic biologics.[2] The third problem of complexity and high costs will likely limit but not blockade entry of generics.

Biologics differ from pharmaceuticals in many respects. Pharmaceuticals are small molecules, can be chemically synthesized, and are orally available. Biologics are large molecules, are created through biologic processes such as fermentation or cell culture then purified, and require special delivery systems such as injections into the bloodstream because they are readily degraded by the digestive system. Manufacturing biologics is more variable and costly than manufacturing pharmaceuticals and includes expensive biologic process development in conjunction with the FDA. Regulators might require extensive clinical testing of generic biologics to demonstrate equivalence to the branded product.

Ours is the first published study that models the generic biologic market from an economic perspective.[3] There is, however, an important body of work in economics on market entry and competition (e.g., Bresnahan 1989, Bresnahan and Reiss 1991). Furthermore, there has been a focus on entry and competition in the generic

[2] The European Agency for the Evaluation of Medicinal Products (EMEA) has begun issuing guidelines for biologically similar products with an anticipated modest reduction (relative to branded products) in clinical trials (Frost and Sullivan 2005). Australia was the first developed country to approve a generic biologic; Omnitrope was approved by the Australian Therapeutic Goods Administration in October 2004. Sandoz used the same data to file for approval of Omnitrope in Australia and the United States, but the FDA indefinitely delayed action on its application pending regulation development (Mathews 2005).

[3] In addition to our research, the Congressional Budget Office and the Office of Management and Budget have been charged with estimating the impact of generic biologics on US government health care costs.

pharmaceutical industry because of its policy relevance and implications for health care expenditures (Caves et al. (1991), Grabowski and Vernon (1992), Scott-Morton (1996),Wiggins & Maness (1996), Frank & Salkever (1997), Reiffen & Ward (2005), Saha et al. (2005)). For example, using data on generic pharmaceuticals from the early 1990s, Reiffen and Ward (2005) find substantial differences in entry between large and small markets with large markets more likely to have many entrants and marginal cost pricing. In addition, studies by a Canadian think tank and US Health and Human Services suggest that average prices for generic pharmaceuticals are higher in Canada than in the United States, perhaps because Canada has a smaller market size and higher fixed costs of entry due to regulations (Alonso-Zaldivar 2005 and Skinner 2005).

In previous studies of generic pharmaceutical manufacturers, one or two entrants had only limited impact on prices; it was the entry of multiple generic firms that was responsible for the substantial differences in prices between branded and generic products in the US market. Will the generic biologic market induce sufficient entry to drive down prices? To assess this question we must consider entry decisions by firms when examining whether to produce a specific generic product. When considering such an investment, firms consider fixed costs, variable costs, and market size. If firm entry in the generic biologic market is not as vigorous as for pharmaceuticals, then price discounts for generic biologics will be smaller than for pharmaceuticals.

We combine a theoretical model of generic biologics with regression estimates from generic pharmaceuticals to estimate market entry and prices in the generic biologic market. We find that generic biologics will have higher fixed costs from clinical testing

and from manufacturing, so there will be less entry than would be expected for generic pharmaceuticals. With fewer generic competitors, generic biologics will be relatively close in price to branded biologics.

Consider a half-billion-dollar product 12 months after the entry of the first generic manufacturer. If generic biologics are like generic pharmaceuticals, except that fixed costs for biologics are 150% higher, then we estimate that there would be 9 generic pharmaceutical manufacturers but only 2 generic biologic manufacturers. With 9 entrants the generic price would be 44% of the branded price, but with 2 entrants the generic price would be 82% of the branded price. Furthermore, if the fixed costs of generic biologic manufacturers were even higher, fewer competitors would enter and generic prices would be higher too.

The estimates from our model abstract from a number of potentially significant factors and are not intended as a forecast of what will happen in the markets for specific biologic products subject to patent expiration. They are intended to illustrate, however, the very important role that fixed costs are likely to play in determining entry and price competition in the market.

In section 2 we describe our methodology of combining a theoretical model of generic biologics with regression estimates from generic pharmaceuticals to estimate market entry and prices in the generic biologic market. In section 3 we report our results, and in section 4 we discuss our findings and consider policy options.

2. Methods

Our methodology can be summarized as follows. First, we characterize the market for generic biologics and solve for elasticity of entry as a function of fixed costs. Second, we compare cost differences between pharmaceuticals and biologics. Third, we estimate market entry for generic pharmaceuticals as a function of market size to inform our understanding of generic biologics. Fourth, we estimate relative prices for generic pharmaceuticals as a function of the number of manufacturers. Fifth, we use the theoretical model and empirical findings to simulate market entry and prices for generic biologics.

Theory of Monopolistic Competition

We model the market for generic biologics in order to better understand how manufacturers respond to changes in market structure such as costs. We characterize the market for generic biologics as monopolistic competition (Chamberlin 1933). The market is competitive in that there is free entry and exit. Of course, the FDA regulates entry of generics, but it does not limit the total number of generics. Because of free entry, in the long run we do not expect generic manufacturers to earn above-normal profits in a particular therapeutic molecule. We expect that generic manufacturers will continue to enter the market until the expected profits for a given product are normal. The market is not, however, perfectly competitive; there are significant entry costs on the supply side of the market.

The focus of our theoretical modeling is to analyze how these costs affect entry and in turn how entry affects the equilibrium of generic price relative to the pre-entry monopoly price. The price ratio is a key dependent variable of interest in our empirical analysis. In our theoretical model, we abstract from strategic behavior on the part of the branded firm. In particular, we assume the branded and generic firms are producing an undifferentiated product and hence only one price will prevail in the long term equilibrium. This equilibrium price will be determined by the zero profit conditions for entrants in our model.[4]

We model the market using a simple inverse demand function, $p=a-b\,Q$, where p is the price and Q is the sum of the output produced by N identical firms. The cost facing firm i is $C(q_i) = m\,q_i + F$ where m is the constant marginal cost and F is the fixed cost. We can solve for a firm's best response function: $q_i = (a-m-b(N-1)q_j)/2b$ where q_j is the output of one of the other $N-1$ identical firms. Given this symmetry, $q_i^* = (a-m)/(b+b\,N)$. Setting profits equal to zero (due to free entry) and solving for N yields the following:

$$N^* = \frac{a-m}{\sqrt{b}\sqrt{F}} - 1 \qquad (1)$$

According to equation 1, the equilibrium number of firms decreases with fixed costs and marginal costs. An important difference between pharmaceuticals and biologics is the

[4] Brand loyalty, buyer inertia, and other demand side effects could lead to divergences in the dynamic path of prices across firms and even "harvesting strategies" in which branded prices increase in the post-entry period (Frank and Salkever, 1997). The potential role of early mover advantages and demand side differences across firms are considered under topics for further research.

cost of production. If fixed costs (F) or marginal costs (m) are higher for biologics, then equilibrium market entry (N^*) will be smaller for a given level of sales.

Figure 1 illustrates the equilibrium. Free entry increases the number of manufacturers until each manufacturer's inverse demand function is tangent to its average cost function. At this output (q_i^*), each manufacturer earns normal economic profits and entry ceases.[5]

We calculate the elasticity of entry, η, which is the percentage change in the equilibrium number of generic entrants 12 months after patent expiration in response to a 1% increase in fixed costs:

$$\eta = \frac{F}{N^*}\frac{\partial N^*}{\partial F} = \frac{-(a-m)}{2(a-m-\sqrt{b}\sqrt{F})} \qquad (2)$$

Given that $b,F > 0$, it follows that $\eta \leq -0.5$. Not only is -0.5 an upper bound for the elasticity and thus a conservative estimate it is also a reasonable estimate. The generic pharmaceutical industry is characterized by high value, relatively low prices, and low costs of entry and manufacturing, so it is reasonable to assume that in the generic pharmaceutical industry $\sqrt{b}\sqrt{F}$ is small. For example, if the maximum willingness to

[5] An alternative model would allow the branded firm to commit to high output and low price and thus deter entry by generics. This pre-emptive strategy has not been observed in the case of generic pharmaceuticals, but other life cycle management strategies such as line extensions and authorized generics have been employed. These are discussed in the section on qualifications and future research.

pay is \$6000 per year (\$500 per month), b=-0.1, and fixed costs are \$1 million then the elasticity of entry is -0.53. If fixed costs are smaller and/or willingness to pay is greater then the elasticity approaches -0.5. An entry elasticity of -0.5 implies that if fixed costs rise by 10% then the equilibrium number of generic firms decreases by 5%.

We have demonstrated that higher fixed costs decrease firm entry. We now consider the impact of higher costs on prices. When firm entry is in equilibrium, the profit-maximizing price for a generic manufacturer is $p_g^* = m_g + \sqrt{b}\sqrt{F}_g$. When the branded manufacturer is a monopolist (N=1) then the profit maximizing price is $p_b^*=(a+m_b)/2$. In equilibrium the ratio of the generic price after patent expiration to the branded price pre-patent expiration is:

$$\frac{p_g^*}{p_b^*} = \frac{2(m_g + \sqrt{b}\sqrt{F_g})}{a + m_b} \tag{3}$$

From equation 3 we see that an increase in marginal costs for generics (m_g) or a decrease in marginal costs for branded drugs (m_b) leads to higher generic prices relative to branded prices. If, however, marginal costs are comparable for generic and branded products, then the impact of marginal costs on the price ratio will be muted, because marginal costs appear in both numerator and denominator. On the other hand, the impact of higher fixed costs is not offsetting. An increase in fixed costs for generics (F_g), leads to an increase in prices for generics relative to branded products (p_g^* / p_b^*) because high fixed costs deter generic entry and diminish competition. An increase in fixed costs for branded products does not affect the price ratio (conditional on branded entry). Hence, when comparing

generic pharmaceuticals to generic biologics, we expect that higher marginal costs for biologics to have a muted effect on the price ratio and higher fixed costs for biologics to have a substantial effect on the price ratio.

Fixed Costs

We examine three fixed costs: clinical trials, capital costs, and manufacturing. We expect that all of these fixed costs will be higher for generic biologics than for generic pharmaceuticals. First, FDA approval will require more clinical testing for generic biologics than for generic pharmaceuticals. For pharmaceutical generics, demonstrating bioequivalence with the branded product is sufficient. In biologics, "the process makes the product," meaning that minor modifications in a bioprocess can lead to variations in quality and safety. Hence, the FDA could require clinical trials in order to demonstrate that generics have sufficiently similar safety and efficacy with the branded products. The average phase III study for branded pharmaceuticals to gain FDA approval costs $86 million and typically enrolls several thousand patients (DiMasi et al. 2003). Even if the phase III study that is required for generic biologic approvals only involves several hundred patients, it would still increase entry cost by many millions of dollars compared to the costs normally incurred under the bioequivalence requirements for generic pharmaceuticals. Furthermore, there would be an opportunity cost given that development time could be 5 to 8 years (1 to 2 years for cell biology, 1 year for process analysis, 2 to 4 years for clinics, and 1 year for approval) (Bio Generix 2005). Generic manufacturers will try to decrease their clinical trial obligations by identifying the

structure and content of biologic molecules using technology such as mass spectrometry and crystallography (Abboud 2005).

Second, capital investment outlays will be significantly greater for generic biologics than for generic pharmaceuticals. Facility construction can take 4 to 5 years and cost $250 to $400 million (Molowa 2001), though this fixed cost might be spread over multiple products. In addition, firms can enter into partnership agreements based on geographical locations. Some facilities could be located in China, India, or Singapore to reduce unit labor costs, but facility costs in those countries may be comparable to costs in the United States if the manufacturer complies with FDA standards. An alternative to manufacturing in-house is contract manufacturing. Due to current scarcity of capacity, however, contract manufacturers have considerable leverage in negotiations and are selective in choosing projects (Molowa 2001). Contract manufacturers are more likely to use their limited capacity to continue relationships with innovators than to ally with generics (Polastro and Little 2001). Eventually, greater capacity will be available, but contract manufacturing for generic biologics will still be more costly than for pharmaceuticals due to the high variable cost of production.[6]

Third, process approval and subsequent manufacturing costs are higher for biologics than for chemical entities. Regulators require manufacturers to describe the cell line and demonstrate that it is free of bacteria, fungi, adventitious viruses, and retroviruses. The

[6] Frost and Sullivan (2003) estimated that total worldwide capacity was approximately two million liters in 2003 with planned expansion to three million liters in 2006. Furthermore, contract manufacturers held approximately 65% of worldwide capacity in 2003.

manufacturer must demonstrate freedom from contamination and molecular integrity of the bulk material. Furthermore, the manufacturer must document quantity, potency, purity, sterility, and stability of the final product. Reproducibility and variability of each assay must be documented using defined procedures. Any changes in the approved manufacturing protocol require rigorous physicochemical characterization of the product and in vitro functional comparisons. Even after FDA approval, if a firm adjusts its manufacturing process, it might be required to complete additional clinical trials (Molowa 2001).

There is, of course, cost heterogeneity across generic biologics. Some products will be easier to manufacture (e.g., human growth hormone is thought to be one of the easier biologics to manufacture) and some products will have lower clinical requirements (e.g., regulators might not be as concerned about small differences in efficacy for human growth hormone as they are for cancer treatments).

In Table 1 we compare fixed costs for pharmaceuticals vs. biologics. For pharmaceutical generics, we estimate that the fixed cost is around $2 million, based on Reiffen and Ward (2005), who estimated that the cost for research and regulatory approval in the early 1990s was $603,000, and a more recent report in *The Economist* (2005) that the cost is "a couple of million dollars."[7] For biologic generics, we estimate that the fixed cost could be

[7] These estimates are for the costs of performing bioequivalence tests and other procedures to gain FDA approval. Most generic pharmaceutical firms have large plants with multiple products. Hence, fixed costs for manufacturing are already spread over a large number of established generic products and there is typically excess capacity to undertake new product offerings. This situation suggests that fixed costs of

$2 million to more than $200 million. The cost will be on the low end if bioequivalence is sufficient for FDA approval and if contract manufacturing is readily available. The cost will be on the high end if FDA requires testing in humans and if manufacturing costs are high.

We turn now to evidence from the generic pharmaceutical industry on the impact of market size on entry and prices. We will estimate entry and prices for generic biologics based on results from generic pharmaceuticals (below) with an adjustment for fixed costs based on Table 1 and equation 2.

Market Entry for Generic Pharmaceuticals

We use data on generic pharmaceuticals to inform our simulations for generic biologics. For the pharmaceutical market we use IMS Health's Generic Spectra data on 40 pharmaceuticals with patent expirations between 1992 and 1998 as reported in Saha et al. (2005) (Table 2). The sample is limited to oral pharmaceuticals prescribed primarily for outpatients. We estimate parsimonious models to facilitate simulations and transparency.

First we estimate generic pharmaceutical entry as a function of market size.

$$ln\,(N) = B_0 + B_1\, ln(\psi) + B_2\, \rho \qquad (4)$$

manufacturing are low for generic pharmaceutical firms in contrast to the current situation for generic biologics.

According to equation 4, the natural log of the number of generic firms[8] one year after initial generic entry (N) is a function of the natural log of the sales of the branded product prior to generic entry (ψ). We also include an indicator variable for whether the product had restricted use ($\rho = 1$ for Clozaril, Mexitil, Toradol, and Zarontin). [9] Following Saha, et al. (2005) and other researchers, we hypothesize that sales in the pre-entry period will be a key factor positively affecting the number of generic entrants. At the same time, we hypothesize that drugs subject to special usage restrictions will attract less generic entry, ceteris paribus (Saha, et. al., 2005).

Relative Prices for Generic Pharmaceuticals

Next, we can estimate the relative prices for generics given market entry. Using the generic pharmaceutical data from IMS, we regress the natural log of the ratio of the generic price measured one year after the initial generic entry (p_{gen}) to the branded price measured prior to generic entry (p_{brand}) on the number of generic firms for a given

[8] IMS is the source for data on the number of generic competitors and annual sales in the pre-entry period. In other analyses of generic entry (Scott Morton 1996, Reiffen and Ward 2005), the number of abbreviated new drug approvals (ANDAs), which is available on the FDA Web site, serves as a proxy for the number of generic competitors. We observed, however, that the number of generic competitors is typically greater than the number of ANDAs due to licensing agreements between generic firms and "formulators" that supply multiple generic firms with a product (Saha et al. 2005).

[9] Each of these products has special usage restrictions (e.g. requirements to start patients with in-hospital intravenous delivery, weekly monitoring, etc.). These restrictions are mandated by the FDA because of the presence of potentially serious side effects. These products also raise particular liability considerations for generic manufacturers.

molecule (N).[10] The regression equation also controls for time trend (t=1 for 1992, … t=7 for 1998) and for the therapeutic class of a drug , X, as denoted by the dummy variables listed in Table 1.

$$ln\,(p_{gen} / p_{brand}) = B_3 + B_4 N + B_5 t + B_6 X \qquad (5)$$

Equation 5 expresses the log of the price ratio as a function of the number of generic firms.[11] Alternatively, by using equations 4 and 5, the price ratio can be expressed as a function of the pre-generic market size: $p_{gen} / p_{brand} = Exp[B_3 + B_4\, Exp[B_0 + B_1\, ln(\psi) + B_2\, \rho] + B_5\, t + B_6\, X]$.

Under other circumstances, modeling relative prices as a function of the number of firms would raise concerns about endogeneity, because the number of firms might be a function of relative prices. In this case, however, the stochastic nature of FDA approval makes the timing of entry decisions largely an exogenous event. In particular, the firm engages in a regulatory process over time with the FDA concerning the chemical, manufacturing, and bioequivalence studies necessary to gain approval. In many cases, the FDA finds the initial Abbreviated New Pharmaceutical Application (ANDA) deficient and requires additional tests or materials. Approval might require two or three resubmissions (Reiffen & Ward 2005). Between 1992 and 1997 the average annual time between the initial application and approval of ANDAs varied between 1.5 and 3.0 years, with significant

[10] Prices for both the branded and generic firms are measured in dollars per gram of product (Saha et al. 2005).

[11] The semi-log functional form provided a superior explanation of variance (adjusted R^2) compared to a log-log or linear form.

additional variability across firms and products (Saha, et. al., 2005). Furthermore, entry requires time to obtain materials and adequate production, particularly for biologics. Hence, it is unlikely that the number of firms at a point in time is affected by current prices (Reiffen & Ward 2005). This stochastic timing of approvals mitigates the endogeneity problem of measuring the relationship between price and the number of competitors.

Market Entry and Prices for Generic Biologics

The market for generic pharmaceuticals provides insight into the market for generic biologics, but an important difference between pharmaceuticals and biologics is the cost of production. If costs are higher for biologics, then market entry will be smaller for a given level of sales.

We assume that the number of generic entrants at 12 months for biologics is a function of the number of generic entrants for pharmaceuticals multiplied by an adjustment factor so $N_{bio} = N\,(1+\delta N/N)$. From equation 2, $\delta N/N = \eta\ \delta F/F$. From equation 4, $N = e^{B0+B1\psi+B2\rho}$. Substituting yields:

$$N_{bio} = (1+\eta\frac{\partial F}{F})e^{B0+B1\psi+B2\rho} \tag{6}$$

The number of generic entrants at 12 months for biologics is a function of the elasticity of entry (η), the percentage change in fixed costs in moving from pharmaceuticals to

biologics ($\delta F/F$), the parameter estimates from the pharmaceutical regression (B_0, B_1, B_2), market size (ψ), and restrictions on product use (ρ).

We now consider the ratio of the generic price to the branded price 12 months after the first generic entry. We take the price ratio from equation 5 (for the pharmaceutical industry) for a given number of generic biologic manufacturers N_{bio} from equation 6. For biologics:

$$\frac{p_{gen,bio}}{p_{brand,bio}} = Exp[B_3 + B_5\, t + B_6\, X + B_4\ (1+\eta\frac{\partial F}{F})e^{B0+B1\psi+B2\rho}] \tag{7}$$

In equation 7, the price of a generic biologic relative to the branded price depends upon the year (t), therapeutic class (X), elasticity of entry (η), the percentage increase in fixed costs over pharmaceuticals ($\delta F/F$), pre-generic market size (ψ), and restrictions on product use (ρ).

3. Results

Generic Pharmaceutical Entry

We find that the number of generic pharmaceutical manufacturers is increasing with market size and decreasing with restrictions on product use, and both variables are statistically significant (Table 3). Because the regression is in logs, the coefficient can be interpreted as an elasticity. For a product with no restrictions, a 10% increase in the level of branded sales prior to patent expiration leads to a 4% increase in the number of generic manufacturers in the market 12 months after the first generic entrant. We also added therapeutic class dummies and a time trend in a separate set of regression estimates.

However, because these variables were insignificant (with t-values less than 1) and the other results unchanged, we did not report these results in the table.

Generic Pharmaceutical Prices

We find that the generic price is closer to the branded price when there are fewer entrants (Table 4). The results imply that the average generic-to-brand price ratio is 90% with one entrant, 63% with five entrants, and 40% with ten entrants. These estimates are at the sample means for the time trend and class dummy variables. We also find that generic prices are relatively lower in later periods and that relative prices vary by therapeutic class, including higher relative prices for generic anti-infectives. This latter finding may reflect the acute nature of treatment for anti-infectives. Some researchers have found more intensive price competition for chronic compared to acute therapies (Lu and Comanor 1998).

Generic Biologic Entry

In Figure 2 we plot the estimated market entry for generic pharmaceuticals as a function of market size prior to generic entry using the results from the first regression. We anticipate that the curve will be lower for generic biologics, but the extent to which it is lower depends upon the increase in fixed costs and on the elasticity of entry. The dashed lines illustrate generic biologic entry if the entry elasticity (η) equals -0.5 and if fixed costs are 100% or 150% higher for generic biologics. We consider the 100% case to be an upper bound for entry because the fixed costs would likely be considerably higher.

There are a number of blockbuster biological products with annual sales of $1 billion now facing patent expiration (Humphreys 2004). In Figure 2, if the pharmaceutical market size is $1 billion, then we expect that on average 12 generic pharmaceutical manufacturers would enter by the end of the first year of generic competition. If fixed costs were 100% higher, our model predicts 6 generic firms would enter, and if fixed costs were 150% higher (still a conservative estimate), 3 generic firms would enter. In the next section we consider the impact of this limited generic competition on generic prices.

Generic Biologic Prices

In Figures 3 and 4 we plot the estimated ratio of generic price to branded price 12 months after generic entry with the time trend set at the midpoint and the therapeutic class variables set at their sample means (i.e., effectively a weighted average of the estimates across all the classes).

In Figure 3 the price ratio is a function of the number of generic manufacturers. In the aforementioned example of a $1 billion dollar product, if there are 12 generic manufacturers, then generic prices are expected to be only 33% of branded prices, but if there are 3 manufacturers, then generic prices are expected to be 75% of the branded price. For the case of one generic entrant, which could prevail in many large biologic markets for a lengthy period of time, generic prices would be 90% of the branded price, given the estimates in our model.

Because the number of manufacturers is a function of market size, we can plot the price ratio against market size as in Figure 4. In Figure 4 we also simulate the market for

generic biologics using equation 7 and the regression coefficients. Again, the dashed lines illustrate generic biologic entry if the entry elasticity (η) equals -0.5 and if fixed costs are 100% or 150% higher for generic biologics.

4. Discussion

Generic pharmaceuticals provide substantial financial benefit to individual consumers and third-party payers in the United States. The generic pharmaceutical industry was stimulated by the Hatch-Waxman Act and now represents more than 50% of the US prescription pharmaceutical market by volume. Given the benefits of generic pharmaceuticals in the United States, policy makers are exploring whether consumers will receive the same benefits from the development of a regulatory framework for generic biologic products.

Generic pharmaceuticals provide a substantial price discount over branded products. Nevertheless, it is not the mere presence of a generic product in the market but competition between multiple firms that results in aggressive price competition and discounting. To assess the potential economic advantages to consumers from generic biologic products we must assess the potential for firm entry into this new market and whether competition among manufacturers of generic biologics is likely to be as vigorous as that of manufacturers of generic pharmaceuticals. In this paper, we predict firm entry based on models of monopolistic competition. In these models, market entry is related to the fixed costs of development as well as potential revenues from market entry.

Since the specific requirements for generic biologic products do not yet exist, we developed a framework for assessing the initial investment required for firms to enter this market. Here, there may be substantial differences between generic pharmaceuticals and generic biologics. Most policy experts anticipate that generic biologics will entail some clinical testing in humans, a process that will require substantially more investment than bioequivalence testing for generic pharmaceuticals.

In our model, entry was limited by high fixed costs, which decreased expected returns. Entry might also be limited by capacity constraints. Although there are exceptions, companies tend to specialize in either pharmaceuticals or biologics due to substantial differences in manufacturing, clinical trials, and regulatory approval. Furthermore, companies tend to specialize in generics or branded pharmaceuticals because of differences in culture and consistency of message. In the case of conjugated hormonal contraceptives, for example, only a handful of generic firms have entered the market, and even the most widely used products have only 2 or 3 generic competitors. If these types of specializations persist, we might anticipate that the market for generic biologics will be filled in part with start-ups. However, start-ups will have trouble raising capital to cover the high fixed costs of entry. Thus, in the short run, entry and output could be limited by a dearth of manufacturers and capacity constraints of those manufacturers, unless contract manufacturing fills this gap.

The availability of contract manufacturing will affect costs and prices. Manufacturing biologics typically requires the development of specific production facilities and certified processes, a substantial difference from the inorganic chemistry and bulk production

techniques of pharmaceutical manufacturing. If generic firms were required to develop their own production facilities, this would have a substantial negative impact on entry (beyond our current estimates). If contract manufacturing is available in the market, the fixed component of the contract price could be substantial, but not as great a barrier as the full cost of internal manufacturing capacity.

We expect the aforementioned factors to reduce entry and price competition in the marketplace, relative to generic pharmaceuticals. Over a considerable period of time, manufacturing and regulatory costs might fall due to technological innovation and familiarity by regulators. Under these circumstances, the market for generic biologics would approach that of generic pharmaceuticals, but this is unlikely for the foreseeable future.

Qualifications and Future Research

We used a long-term equilibrium analysis of symmetric generic entrants[12] for the sake of analytical tractability and to illuminate the important role of higher fixed costs on the supply side of the market as a factor limiting generic entry in biologics. A limitation of the study is that we use a one-year horizon in our empirical analysis of generic pharmaceuticals to simulate equilibrium entry and prices. Nevertheless, the assumption that markets in generic pharmaceuticals converge to equilibrium within a year's time is a

[12] In the long run, expected economic profits should be normal, but ex post economic profits might be negative if too many generic manufacturers enter the market. This problem of simultaneity might be mitigated if firms can observe one another's construction of manufacturing capacity and thus credibly deter additional capacity and production by rivals.

reasonable approximation for the case of a large-selling pharmaceutical. This is the primary case of interest in our analysis. In particular, the potential of large sales combined with low costs of entry attracts a large number of entrants and rapid convergence toward equilibrium price levels for generic pharmaceuticals.

Another limitation is that we use elasticities which are best applied to small percentage changes. Here, the difference between fixed costs for generic biologics vs. generic pharmaceuticals could be more than 200%. More insight could be gained from US generic pharmaceuticals with a richer data set enabling a more structural model, but any forecast is likely to be imprecise given uncertainties about regulations and costs for generic biologics.

There are a number of interesting issues to explore in further research concerning demand side factors. First, it would be interesting to explore demand side differences between pharmaceuticals and biologics that could affect entry. In contrast to oral pharmaceuticals, large-molecule injectible biologics are typically dispensed by physicians in clinics or hospitals and for at-risk patient populations with diseases like cancer. In this environment, physicians and providers might be very cautious in embracing generic biologics until widespread market experience demonstrates their safety and efficacy. Consequently, generic biologic firms might find it optimal to invest in substantial physician education and detailing. Indeed, they might even pursue a strategy of branded generics, which would entail extra upfront expenses but also enhance early mover advantages. Detailing and branding are rare for generic pharmaceuticals due to strong economic incentives for physicians, pharmacists, and patients to substitute generics for

the branded alternative (e.g., three tier formularies, mandatory generic substitution, and higher margins to pharmacists for generics).

A second direction for further analysis is the response of the innovator firm to generic biologics. Brand firms have generally eschewed significant price competition with pharmaceutical generics.[13] Rather, they have opted for life cycle management strategies such as the introduction of a new dosage formulation or a shift to over-the-counter status. This might be changing with the emergence of "authorized generic" strategies, particularly in cases where a single generic firm holds 180-day exclusivity as part of a successful patent challenge (Reiffen and Ward 2006). Innovators in biologics, faced with the threat of generic entry, might combine both life cycle management strategies (e.g., new patent-protected product improvements) with authorized generic strategies for earlier-generation products. This is another factor that could affect entry and the equilibrium levels of firms.

[13] The impact of generic entry on branded price is unclear. On the one hand, the branded manufacturer could lower its price to compete with the generic. Alternatively, the branded manufacturer might raise the price because its remaining customers are less price-responsive. Previous researchers have found a small positive effect of generic entry on branded price (Frank & Salkever 1997 and Grabowski & Vernon 1992) or a small negative effect of generic entry on branded price (Caves et al. 1991) (Saha et al. 2005). Bhattacharya and Vogt (2002) found a large negative effect of generic entry on branded prices. In our sample, only Tagamet had a lower price one year after the first generic entry, though some branded manufacturers increased their prices slower than the rate of inflation. Twenty-eight of forty manufacturers increased their prices faster than the rate of inflation (pharmaceutical producer price index).

Policy Options

We assume that regulatory requirements for generic biologics will be driven by safety concerns and will include at least some clinical trial data related to safety and efficacy. We forecast that limited entry in the market for generic biologics will result in generic prices that are relatively close to branded prices. To decrease prices the government could create incentives for greater entry using push or pull mechanisms. Push mechanisms decrease fixed costs (e.g., grants for translational medicine, easing regulations, encouraging contract manufacturing capabilities) whereas pull mechanisms subsidize returns (e.g., 180-day exclusivity for the first generic pharmaceutical). Both push and pull mechanisms use government subsidies to encourage entry and drive down long-run prices.

It is not clear, however, that push or pull mechanisms would enhance social welfare. Consider each of the players. For innovators, returns would fall due to increased generic competition. For generic manufacturers, the expected impact would be neutral because there is free entry and subsidies would drive down both costs and also prices. For taxpayers, lower prices might be offset by the cost of subsidies, particularly if the subsidies pay for duplicative fixed costs. In the presence of economies of scale, it can be particularly inefficient to pay subsidies to reduce fixed costs for multiple manufacturers.

Given uncertainty about the market for generic biologics, it is challenging to accurately forecast the market. Nevertheless, we can use economic theory and empirical observation of generic pharmaceuticals to gain a better understanding of the likely market for generic biologics. We find that high fixed costs of entering the market for generic biologics will

create less entry than would be predicted for generic pharmaceuticals. We also expect that generic biologics will be relatively close in price to branded biologics for the foreseeable future. Policy makers should be cautious in projecting large financial benefits from generic biologics for consumers and payers based on the experiences of generic pharmaceuticals. They should consider how generic biologics will differ in terms of economics as well as scientific and regulatory factors.

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Table 1: Components of fixed costs for generics

Clinical research	Pharmaceuticals	Biologics
	Bioequivalence	Might require human testing
Regulatory	Licensure	Licensure
Manufacturing	Clinical process • existing capacity within firms • contract manufacturing available	Biologic process • high fixed costs • questionable availability of contract manufacturing
Total fixed costs	$2 million	$2 million (bioequivalence, manufacturing availability) to more than $200 million (human testing, high manufacturing costs)

Table 2: Generic Pharmaceutical Data

Product	Class	Generic Launch	Market Size at Entry (in 2000 $ m)	Generic Share 12 Months after Generic Entry	Generic Price 12 Months after Generic Entry to Branded Price Pre-Entry	Number Generics 12 Months after Generic Entry
Zantac	Gastrointestinal	Jul-97	1,856.94	75%	34%	13
Tagamet	Gastrointestinal	May-94	875.40	66%	46%	19
Xanax	Psychotherapeutic/sedative	Sep-93	805.49	72%	10%	20
Naprosyn	Analgesic	Sep-93	697.05	85%	17%	18
Ceclor	Anti-infective	Oct-94	656.71	83%	73%	8
Capoten	Cardiovascular	Dec-95	639.75	79%	5%	21
Zovirax	Anti-infective	Apr-97	573.37	86%	44%	20
Cardizem	Cardiovascular	Oct-92	557.67	64%	26%	13
Lopid	Cardiovascular	Jan-93	539.03	63%	67%	8
Klonopin	Neurological disorder	Sep-96	395.95	72%	70%	3
Lopressor	Cardiovascular	Oct-93	371.26	58%	33%	13
Lodine	Analgesic	Feb-97	343.83	59%	51%	12
Voltaren	Analgesic	Aug-95	331.17	81%	64%	6
Glucotrol	Diabetes	May-94	288.60	58%	64%	10
Clozaril	Psychotherapeutic/sedative	Dec-97	281.73	10%	65%	1
Diabeta	Diabetes	Apr-94	263.43	77%	61%	7
Sinemet	Neurological disorder	Jan-93	205.89	28%	63%	9
Corgard	Cardiovascular	Aug-93	185.32	45%	79%	4
Carafate	Gastrointestinal	Nov-96	159.72	66%	66%	2
Ansaid	Analgesic	Jun-94	154.97	72%	60%	5
Orudis	Analgesic	Dec-92	145.02	62%	40%	12
Lozol	Cardiovascular	Jul-93	143.41	42%	75%	2
Eldepryl	Neurological disorder	Aug-96	118.84	41%	41%	6
Tenoretic	Cardiovascular	Jul-92	101.50	39%	67%	6
Dolobid	Analgesic	Oct-92	98.29	58%	51%	9
Parlodel	Neurological disorder	Jan-98	82.91	33%	69%	3
Halcion	Psychotherapeutic/sedative	Sep-93	74.78	50%	63%	9
Bumex	Cardiovascular	Jan-95	69.64	34%	77%	4
Anafranil	Psychotherapeutic/sedative	Dec-96	59.43	67%	49%	5
Toradol	Analgesic	May-97	50.89	70%	65%	2
Visken	Cardiovascular	Oct-92	50.06	34%	58%	10
Sectral	Cardiovascular	May-95	47.71	46%	72%	1
Mexitil	Cardiovascular	Jun-95	42.42	40%	66%	5
Capozide Cardiovascular	Cardiovascular	Dec-97	39.80	48%	39%	5
Cardene	Cardiovascular	Jul-96	27.47	40%	62%	4
Wytensin Cardiovascular	Cardiovascular	Sep-94	15.30	43%	56%	6

Prosom	Psychotherapeutic/sedative	Jul-97	14.97	44%	63%	3
Aventyl	Psychotherapeutic/sedative	Jul-92	13.60	97%	64%	1
Zarontin	Neurological disorder	Aug-94	11.92	1%	75%	1
Vivactil	Psychotherapeutic/sedative	May-96	6.55	26%	66%	3
Mean			**285**	**55%**	**55%**	**8**

Source: IMS Generic Spectra audit data as reported in Saha et al. (2005).

Table 3 – Results from Generic Pharmaceutical Entry

The dependent variable is the natural log of the number of generic manufacturers of a given molecule.

Variable	Parameter Estimate	Standard Error	p-value
Intercept	0.07	0.40	0.86
Log of the market size	0.36	0.08	<.0001
Restricted use	-0.90	0.35	0.01

Adjusted R^2 = 0.46

Table 4 – Results from Generic Pharmaceutical Pricing

The dependent variable is the natural log of the ratio of the generic price to the branded price. Psychotherapeutic/sedative is the omitted therapeutic class.

Variable	Parameter Estimate	Standard Error	p-value
Intercept	0.00	0.20	1.00
Number generic manufacturers	-0.09	0.01	<.0001
Time trend	-0.05	0.03	0.10
Analgesic	0.23	0.18	0.21
Anti-infective	0.93	0.28	0.00
Cardiovascular	0.08	0.15	0.59
Diabetes	0.46	0.26	0.09
Gastrointestinal	0.52	0.23	0.03
Neurological disorder	0.16	0.19	0.41

Adjusted R^2 = 0.65

Figure 1. Free entry increases the number of manufacturers until each manufacturer's inverse demand function is tangent to its average cost function. At this point (qi*), each manufacturer earns normal economic profits and entry ends.

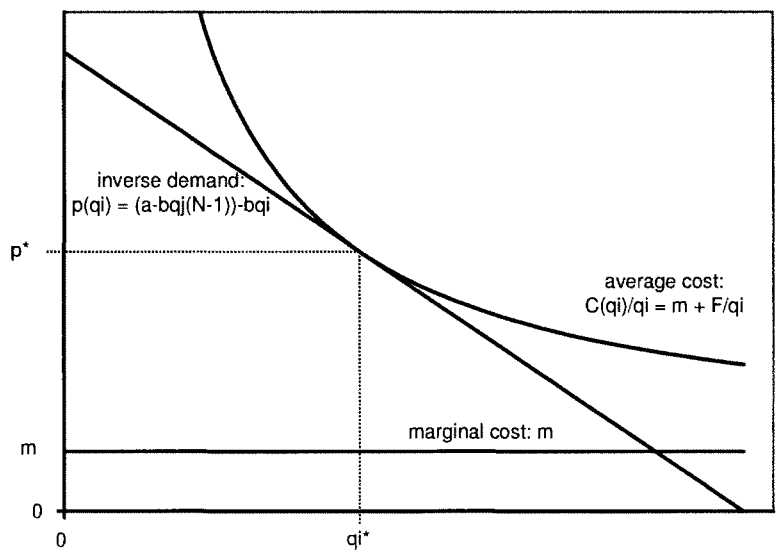


Figure 2. Estimated number of generic manufacturers 12 months after the first generic entry as a function of branded market size ($ million) prior to generic entry.

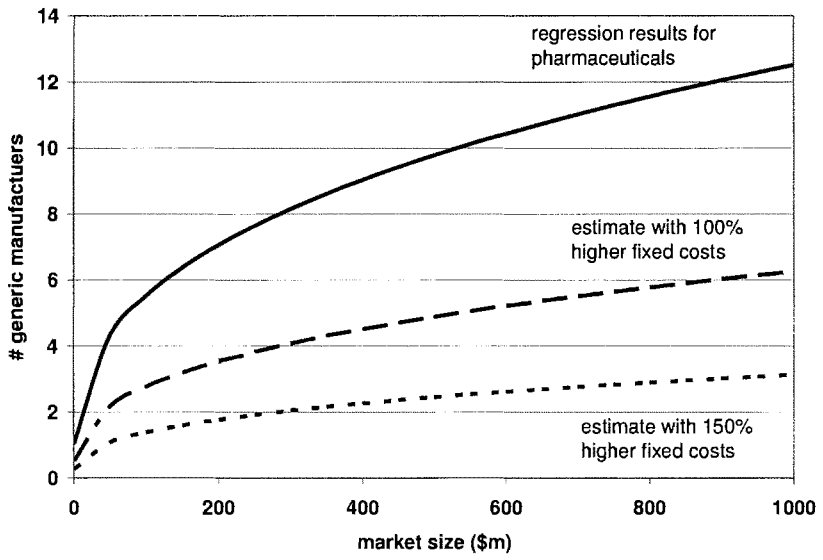


Figure 3. The ratio of generic price to branded price as a function of the number of generic manufacturers.

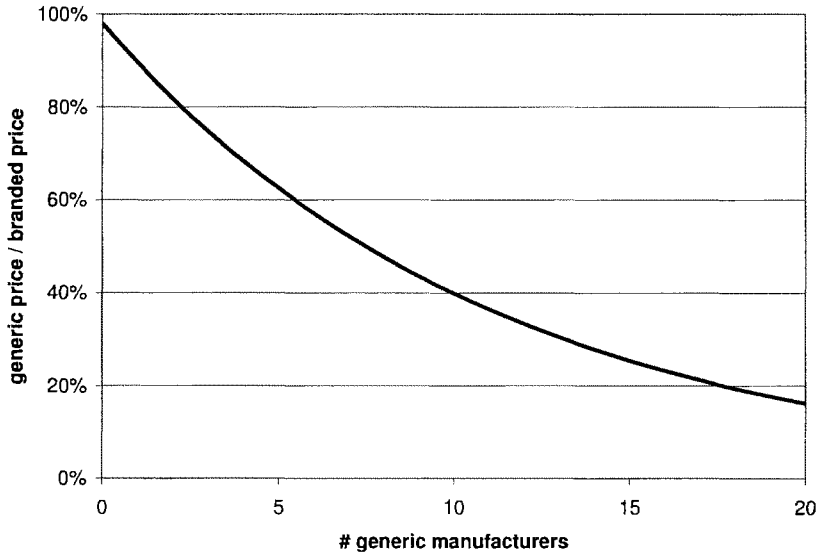
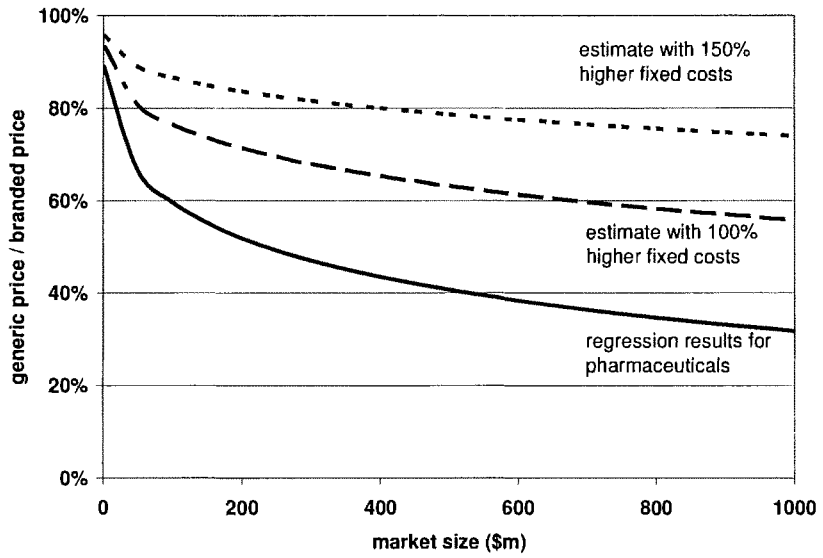


Figure 4. The ratio of generic price to branded price as a function of market size.



The Market For Follow-On Biologics: How Will It Evolve?

The market for biologically derived treatments differs in important ways from the market for chemically derived drugs.

by Henry Grabowski, Iain Cockburn, and Genia Long

ABSTRACT: With spending on biologics rising and patent expiry approaching for several blockbuster biologics, Congress and the Food and Drug Administration are considering creating a clear pathway for so-called follow-on biologics. Differences between drugs and biologics will affect market outcomes in various ways. Conservative budget impacts are appropriate in the short run because fewer competitors will enter, and average prices will drop less than was the case following the Hatch-Waxman Act. Over the long term, intellectual property provisions will be important considerations for policymakers designing a pathway for follow-on biologics that balances price competition and innovation incentives. [*Health Affairs* 25, no. 5 (2006): 1291–1301; 10.1377/hlthaff.25.5.1291]

BIOLOGICS REPRESENT A SIZABLE SEGMENT of the U.S. drug industry, with sales expected to exceed $60 billion by 2010.[1] Because these products are growing at twice the rate of prescription drugs (2004), health plans, employers, and government insurers have concerns about their potential financial impact, while patients are concerned about continued access to potentially beneficial therapies. With patents for a number of blockbuster biologics (medical treatments derived from living organisms) expiring in the next several years, Congress and the Food and Drug Administration (FDA) are under pressure to enable the expedited approval of so-called follow-on biologics (also referred to as biogenerics or biosimilars), thus paving the way for the development of a robust U.S. follow-on biologics industry, following the lead of the Hatch-Waxman Act for generic drugs.

Proponents of an approach similar to that embodied in Hatch-Waxman make several assumptions about its economic impact: First, there will be many entrants, and competition will be based primarily on price; second, prices will drop substantially, and consumers will have better access to biologics; and third, incentives for innovation will not weaken. However, the market for follow-on biologics might develop differently from that for generic drugs for a number of reasons.

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We examine important differences between biologics and drugs that could affect market outcomes. We then consider how the market is likely to evolve, conditional on the regulatory environment, technological and marketing barriers to entry, and market acceptance. We also point out some important open policy questions and identify priority areas for further empirical investigation.

The Hatch-Waxman Act And Biologics

The Drug Price Competition and Patent Term Restoration Act of 1984 (often referred to as the Hatch-Waxman Act) established the Abbreviated New Drug Application (ANDA) process for generic drug approval. In reviewing ANDAs, the FDA relies on a prior finding of safety and efficacy for a referenced pioneer drug, with a generic applicant having only to demonstrate bioequivalence between its product and the referenced drug.[2] Prior to 1984, generic drugs were subject to the same approval requirements as innovator drugs.

Although the Hatch-Waxman Act provides a clear path for generic drug market entry, it generally does not apply to biologics. Drugs are regulated by the federal Food, Drug, and Cosmetic Act (FD&C Act), and biologics are generally regulated under the Public Health Service Act (PHS Act), which has no equivalent provision to the ANDA allowing the expedited approval of generic versions of approved, on-market products. Some early biologics, such as human growth hormone (hGH), insulin, and conjugated estrogens, were approved as drugs under the FD&C Act. ANDAs could be approved for these products, subject to FDA resolution of the scientific and other issues involved.[3] However, congressional action will be required before follow-on versions of biologic products regulated under the PHS Act can be approved by the FDA. Congress and the FDA are considering various scientific and legal issues surrounding follow-on biologics, to define a regulatory process for them.

Biologics are typically more complex molecules than chemical drugs; they are not manufactured through chemical synthesis but instead are produced through biological processes involving manipulation of genetic material and large-scale cultures of living mammalian, microbial, or yeast cells. Biologics made in different cell lines or manufacturing plants might behave differently as medicines and exhibit unexpected adverse events in vivo. These basic differences in turn lead to important differences in the economics of discovery, development, manufacturing, and distribution for drugs and biologics. Consequently, this could lead to different economic outcomes in terms of average prices, number of competitors, returns on spending for research and development (R&D), and other market measures.

Economic Analyses Of Pharmaceuticals And Biologics

■ **Innovators' R&D costs.** A number of studies have investigated the average cost to discover and develop a new drug. Joseph DiMasi and colleagues estimate R&D costs at $403 million per new drug in an oft-cited study.[4] When capitalized to

the point of marketing approval at a real discount rate of 11 percent, the total preapproval cost is $802 million (in 2000 dollars).[5] Although the sample of biologics in this study was small, the limited data suggested that development costs were similar for biologics and drugs.

A recent analysis by DiMasi and Henry Grabowski examined the R&D costs for a data set of recombinant proteins and monoclonal antibodies.[6] The authors assembled drug-specific data on R&D costs by phase of development for a sample of seventeen biologic products drawn from these two categories. These data were integrated with a larger database on transition probabilities and development times for new biologics. The authors found that the R&D costs for new biologics are comparable in magnitude to DiMasi and colleagues' previous estimates for drugs (after adjustments were made for the different time periods covered by the two studies).[7] However, they also found that the underlying R&D cost components differed substantially between new biological entities and drugs. Specifically, biologics realized higher probabilities of clinical success (30 percent compared with 21.5 percent for new drugs) but also experienced longer mean clinical development times (ninety-eight versus ninety months). These findings are consistent with earlier analyses of these parameters.[8]

The DiMasi-Grabowski study also suggests that the development of biologics entails higher manufacturing process costs than is true for drugs. This reflects the need to resolve novel manufacturing challenges at the R&D stage for products developed through fermentation or fragile mammalian cell cultures. By contrast, manufacturing process issues in R&D are more straightforward for new chemical drugs. Process specifications and know-how will be important for the FDA to consider from both a regulatory and an intellectual property (IP) perspective in developing guidelines for follow-on biologics.

■ **Imitators' R&D costs.** It remains to be seen what the regulatory requirements will be for follow-on biologics. Given that biologics made with different cell lines or manufacturing facilities might exhibit different efficacy and safety characteristics, it is likely that some clinical trial data will be required before a follow-on biologic is approved. New follow-on entrants might not have to repeat all of the original sponsor's clinical steps or incur the costs associated with large Phase III clinical trials. However, even relatively small trials of biologics in a few hundred patients are likely to cost tens of millions of dollars and take several years to complete. In the case of European approvals, some generic companies' estimates suggest that a plausible range could be $10–$40 million.[9] The exact amount is likely to depend on how well-characterized the molecule is and on other scientific and technological factors. This contrasts with the $1–$2 million cost and approximately two years necessary to demonstrate bioequivalence for generic drugs.[10]

While Congress and the FDA consider the legal and scientific framework for follow-on biologics, branded competition for biopharmaceuticals such as hGH and recombinant insulin has emerged using the New Drug Application (NDA)

regulatory pathway. In the case of hGH, six manufacturers are approved for marketing in the United States.[11] These manufacturers received FDA approval under separate NDAs by conducting their own comprehensive Phase III studies to demonstrate efficacy and safety. The products are not rated as bioequivalent by the FDA and cannot be substituted for each other, although managed care plans might view them as undifferentiated. Competition in hGH is also multidimensional: Products are marketed under separate brand names and compete on price, promotion, and product differentiation (for example, with different delivery systems such as pen dispensers). Follow-on biologics might retain some elements of this competition, as discussed further below.

■ **Manufacturing cost and risk.** The required capital investment in property, plant, and equipment and the costs of manufacturing are also likely to be higher for follow-on biologics than for generic drugs. Cell culture facilities require sizable capital and labor investment, taking, on average, three to five years to construct and costing $250–$450 million. Investment in manufacturing plants must often be made before drugs enter clinical testing. Cost of materials is also high; in 2002 these materials cost twenty to one hundred times more than those used for drugs.[12]

■ **Market size.** As in the market for drugs, the sales distribution of biologics is highly skewed, with relatively few compounds accounting for a disproportionate share of sales and profits. Of thirty new biologics introduced from 1982 to 1994, one-fifth accounted for roughly 70 percent of total 2002 sales.[13] Biologics in the top quintile or decile of sales will attract the most interest from follow-on manufacturers. Several studies have established that the number of entrants for generic drugs is strongly related to the size of the brand-name product's sales prior to entry.[14]

It is also relevant that many biologics have been "niche drugs" targeting rare conditions and small numbers of patients. As a result, during 1983–2001, biotech firms accounted for two-thirds of the research on orphan drugs—whose estimated maximum U.S. markets were no more than 200,000 patients—although they represented fewer than half of FDA approvals.[15] Among these products, only those with sizable revenues would be expected to attract generic competition.

■ **Product margins.** Average net income as a percentage of gross revenue and gross margin percentage for mature biotech companies approximate those of major pharmaceutical manufacturers, although the distribution of expenses differs somewhat, with a higher percentage of gross revenues to R&D and lower percentage to sales, marketing, and administrative costs.[16] However, there are few such companies. The universe of biotech firms is populated with development-stage companies. Most are not profitable, and the variance of such financial statistics is greater than for the pharmaceutical industry. The market structures of the two industries are therefore very different.

■ **Distribution structure and supply-chain incentives.** Markets for biologics and drugs also differ in the structures of their distribution systems and in the economic incentives for participants in the value chain. Most drugs are oral agents dis-

"Changes in regulation could lead to hard-to-predict long-term effects on capital investment in the biotech industry."

tributed through retail and mail-order pharmacies. Strong financial incentives and systems favor rapid generic penetration. Managed care plans adjudicate and budget for these claims as pharmacy benefits. They have implemented strong formulary management systems, including preferred formulary status and lower copayments for or mandatory use of generics. Financial incentives for drug retailers also favor rapid generic drug substitution, because they often earn higher gross profit margins on generic drugs than on brand-name drugs.[17] Medicare Part D drug plans will extend these incentives for generic drug penetration with formulary designs that are at least as aggressive as those in their current commercial lines of business.

In contrast, biologics include both injected or transfused agents delivered in a physician's office, clinic, or hospital and self-injectible products dispensed through pharmacies. Medicare reimbursement for infusions delivered in clinics and physicians' offices historically has been maintained at artificially low levels, resulting in the need for cross-subsidies between these rates and the spread between average wholesale price (AWP) and actual acquisition cost. This has been addressed somewhat by increasing procedure reimbursement, decreasing infused-agent reimbursement with the shift in January 2005 from AWP- to average sales price (ASP)–based reimbursement, and the recent implementation of the voluntary competitive acquisition program (CAP). The long-term impact on incentives for the substitution of lower-cost products is unknown.[18]

Because many biologic therapies are designed to treat cancer and other life-threatening diseases and might not have close substitutes, managed care organizations in the past have been reluctant to restrict access or to pursue aggressive cost or utilization control processes. Biologics often have been managed within plans as medical benefits, which have been less subject to centralized formulary controls than pharmacy benefits have. This is changing, particularly in indications where there is a choice between multiple brand-name biologics, and tiered formularies reflect considerations of net cost after manufacturer rebates.[19] Increasingly, a fourth tier, which includes expensive biologic therapies and coinsurance rather than copayment, is emerging. These institutional practices will likely accelerate with the introduction of follow-on biologics, but the speed of change will depend on how rapidly concerns about safety can be satisfactorily addressed.

Intellectual Property Considerations

IP provisions in the Hatch-Waxman Act have led to evolving levels of strategic behavior on the part of both generic and brand-name pharmaceutical firms. These provisions also have been the source of much litigation. Specifically, Hatch-Waxman provided an inducement to patent challenges by rewarding the first suc-

cessful generic challengers with 180-day exclusivity. As a consequence, generic firms now follow "prospecting" business models involving patent suits, and virtually all profitable pharmaceuticals face patent challenges after their first five years of market life.[20] Generic entry based on an ANDA can occur after the five-year data exclusivity period expires, but subject to a thirty-month stay on entry while courts adjudicate patent validity and infringement. Brand-name firms also have used various IP provisions to forestall entry, such as multiple stays on entry. Congress addressed this behavior in the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003.[21]

IP is a critical intangible asset for biotech and pharmaceutical firms.[22] Given the entrepreneurial nature of the biotech industry, a higher probability of a successful challenge to a company's patent portfolio could lead to adverse consequences and insolvency for many development-stage biotech companies. This means that changes in regulation could lead to hard-to-predict long-term effects on the complex network of capital investment in the biotech industry. These IP issues are open policy questions that will need to be resolved for follow-on biologics. We discuss some of the trade-offs regarding them later.

How Will The Market Evolve?

Regulatory environment, technology and manufacturing barriers, and market acceptance and competition will determine market outcomes for follow-on biologics. In our opinion, limited competition of either the nonbranded or the branded variety is most likely in the short run because of regulatory conservatism, relatively high barriers to entry, and initial caution on follow-on product acceptance. For the typical drug, generic prices begin to approach their long-run marginal cost when there are at least ten competitors in the market.[23] For commercially successful drug products, there has been sufficient entry to drive prices close to marginal costs within a relatively short period after patent expiration, generally less than a year and, more recently, just a few months. The time required likely will be much longer in the follow-on biologic market than in the generic drug market. The basis for this view is explained below, along with a discussion of some changes that could reduce likely regulatory and institutional barriers.[24]

■ **Regulatory environment.** Until Congress changes the PHS Act to create a process for competition in follow-on biologics, prospective entrants will have to do extensive clinical trials under separate Biological Licensing Applications (BLAs). As discussed above, some biologics approved under the FD&C Act, such as hGH and recombinant insulin, already have multiple competitors based on NDAs, but entry costs are high, and price competition to date could be limited. Sandoz's suit to direct the FDA to act on its 2003 application for the hGH Omnitrope reflects an alternative third route, through Section 505(b)(2) of the FD&C Act, which allows the FDA to rely on the published scientific literature or its previous findings for similar products. In June 2006, the FDA approved Sandoz's application but narrowly circum-

"The recent wave of biologic approvals suggests that there might be limited idle manufacturing capacity in the near future."

scribed its approval to protein products approved under the FD&C Act with a single active ingredient, with a well-understood mechanism of action, and that also could be well characterized with existing technology. Furthermore, Omnitrope is not rated as therapeutically equivalent, or substitutable for, other approved human growth hormone products.[25]

Given the rapid growth in spending on biopharmaceuticals and the extensive number of new products likely to be introduced in the coming years, we expect that Congress will act to create some form of an abbreviated process for follow-on biologics. At the same time, given the uncertainty surrounding safety risks, one would expect that Congress will give considerable discretion to the FDA to determine the extent of any clinical testing that will be required for these approvals. In particular, we expect that the scientific criteria for what constitutes a biosimilar product will be left to the discretion of the FDA.

The FDA has been cautious when a new technology poses potential safety hazards. European regulators are ahead of the United States in developing regulations for follow-on biologics, and the European Agency for the Evaluation of Medicinal Products (EMEA) has indicated a case-by-case approach, with some data on clinical efficacy and safety necessary for market approval. To date, two hGH follow-on products to somatropin, Sandoz's Omnitrope and Biopartners' Valtropin, have been approved in Europe.[26] The FDA could adopt a more restrictive approach than Europe's when incorporating technical guidelines that are applicable to multiple classes of biologics. The recent market withdrawal of two cyclooxygenase-2 (COX-2) inhibitors and the appointment of the special Institute of Medicine Committee to study the impact of FDA procedures on product safety will amplify cautious institutional tendencies on this score.[27]

■ **Technology and manufacturing barriers.** There are also important open issues concerning technology and manufacturing barriers to entry and how rapidly manufacturing costs will decline over time as a result of process innovation.

The recent wave of biologic approvals and expanded pipelines suggests that there might be limited idle manufacturing capacity in the near future. If so, we expect that potential producers of follow-on products would need sizable investments in their own facilities to compete. This would be a major financial hurdle for all but the largest entrants or established generic product manufacturers. The generic product manufacturing industry is undergoing consolidation, but only a few established companies appear capable of undertaking the costs and risks.

Over longer time frames, expansion in manufacturing capacity and technological advances in process engineering could greatly decrease the fixed and variable costs for follow-on biologics. In particular, a new group of follow-on manufactur-

ing "specialists" might emerge, which might be biotech product firms, manufacturing technology platform firms, or established generic manufacturers (either stand-alone manufacturers or generic arms of diversified large pharmaceutical firms). Expanded roles for outsourced manufacturing specialists could emerge, just as Contract Research Organizations (CROs) have "hollowed out" some aspects of clinical development, if they are able to lower manufacturing costs for biologics.

Competition in process technology could drive down costs, ease market access for new products, raise expected returns to upstream firms, and stimulate entry and innovation. However, these gains might or might not be ultimately passed on to patients. Manufacturers or "integrators" who control IP and market access might capture rents, as suggested by the experience of new entrants, which typically share a larger fraction of profits with manufacturing/marketing partners to bring products to market.

■ **Market acceptance and competition.** Market acceptance and competition uncertainties include the substitution rates for existing brand-name biologics and what incentives, reimbursement systems, and marketing expenditures will be needed to encourage rapid substitution.

We expect that users will be cautious with respect to follow-on products in the short term, until clinical experience has accumulated. Some clinical trials will likely be needed to demonstrate that a follow-on product is therapeutically equivalent to the original product. The perspectives of specialist physicians and organized patient groups in therapeutic areas with high usage of biologics will be important in driving or limiting demand for follow-on products.

To overcome barriers to acceptance among physicians and patients, follow-on biologic entrants might find it necessary to establish "reputation bonds" with brand-name products to capture and maintain market share. In this environment, market access is facilitated through specialist education and detailing, as well as through contracts with major health plans and coordination with centralized formulary policies. Relative to generic drugs, companies might have to incur the added costs of professional detailing forces, perhaps comparable to those of specialty drugs and biotech companies (estimated elsewhere at forty people).[28]

The Case Of Combination Hormonal Contraceptives

In considering how market structure in follow-on biologics could evolve, the case of combination hormonal contraceptives might be instructive. The investment costs and technical complexity of establishing bioequivalence are somewhat higher than for other drugs, and entry has been concentrated in a handful of specialty generic firms. Generic contraceptives are certified by the FDA as bioequivalent to the referenced brand, but they are marketed under separate brand names (that is, as branded generics). There are no more than three generic competitors for even the very largest-selling contraceptive drugs.[29] As a consequence, generic

price competition is more limited, relative to other drug classes with comparable market sales.

The barriers to entry can be expected to be greater initially for follow-on biologics than for these hormonal contraceptive products. Hence, we can expect some of the differences observed in this market to be present for follow-on biologics. It is also important to remember that the current rapid pace of generic entry and penetration that now characterizes most drugs with substantial sales when patents expire took many years to evolve. We expect that this also will be true for follow-on biologics.

Discussion And Concluding Comments

In sum, we expect that regulatory conservatism, high manufacturing barriers to entry, and limited acceptance of follow-on products will constrain the number of market entrants, the key driver of lower generic drug prices. A robust follow-on industry is likely to emerge as regulatory standards evolve and demand develops, but this will probably take time, even for some well-characterized biologics.

Consequently, we believe that conservative assumptions are appropriate in "scoring" the budgetary savings from legislation that creates a regulatory framework for follow-on biologics, even assuming that scientific, public health, and safety issues are resolved. Technological advances and institutional changes eventually will facilitate entry by multiple follow-on manufacturers, but this will take time. In the meantime, prices might drop only moderately, but substantial gains could occur for a small number of entrants with the required skills and assets.

When creating a legal framework for follow-on biologics, however, legislators and regulators should adopt a long-term perspective. Over the coming decades, biopharmaceutical innovation can provide major improvements with respect to the quality and length of human life but could also exacerbate cost pressures and access disparities in health care. It will fall to Congress and the FDA to balance the objectives of innovation incentives and price competition, as was the case when Congress created the Hatch-Waxman program more than two decades ago.

The optimal design of a legal framework for follow-on biologics is beyond the scope of this paper. But given the entrepreneurial character of the biotech industry, we think that it is especially important that Congress carefully consider the intellectual property provisions that will govern competition between innovators and imitators. In particular, Congress will have to consider whether to award market exclusivity to the first follow-on biologic to challenge a patent successfully. If it enacts such a provision, it will also need to determine the data exclusivity period for innovators, because this determines the earliest point in time that follow-on biologics can enter based on an abbreviated process that relies in whole or part on innovators' safety and efficacy data.

Intellectual property has been an important factor for biotech start-ups in securing venture funding and partnerships with larger firms. Product life cycles for

new medicines span decades, and R&D decisions are made with long time horizons on future returns. Legislators might view the encouragement of patent challenges and attendant litigation as a good short-term mechanism for exposing more biologics to follow-on price competition. But increased uncertainty and IP litigation in biotech also would have major negative-incentive effects on capital market decisions for developing private and public biotech firms with promising pipelines. Most of these firms have few if any profitable products.

The European Union (EU) recently instituted a ten-year data-exclusivity period for pharmaceutical innovators.[30] This prevents patent challengers from filing applications relying on innovators' safety and efficacy data until at least ten years have elapsed. The comparable period in the United States is five years. Given the high costs and long time required to develop a new medicine, five years is generally not sufficient to cover R&D costs and earn a risk-adjusted return.[31] A longer data-exclusivity period for biologics could be useful for policymakers to consider in their efforts to balance innovation incentives and price competition.

Further investigation and quantitative analysis and simulation would be valuable to policymakers, including the following: modeling the number of market entrants and resulting prices by therapeutic area after follow-on entry; estimating fixed costs of market entry and variable costs of manufacturing, with comparison to generic drugs; identifying likely marketing investments by therapeutic area and their impact on market organization; and estimating long-term effects on R&D investment and innovation and investment risk in the biotechnology sector.

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NOTES

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THE COST OF BIOPHARMACEUTICAL R&D: IS BIOTECH DIFFERENT?

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ABSTRACT

The costs of developing the types of new drugs that have been pursued by traditional pharmaceutical firms have been estimated in a number of studies. However, similar analyses have not been published on the costs of developing the types of molecules on which biotech firms have focused. This study represents a first attempt to get a sense for the magnitude of the R&D costs associated with the discovery and development of new therapeutic biopharmaceuticals (specifically, recombinant proteins and monoclonal antibodies [mAbs]). We utilize drug-specific data on cash outlays, development times, and success in obtaining regulatory marketing approval to estimate the average pre-tax R&D resource cost for biopharmaceuticals up to the point of initial U.S. marketing approval (in year 2005 dollars). We found average out-of-pocket (cash outlay) cost estimates per approved biopharmaceutical of $198 million, $361 million, and $559 million for the preclinical period, the clinical period, and in total, respectively. Including the time costs associated with biopharmaceutical R&D, we found average capitalized cost estimates per approved biopharmaceutical of $615 million, $626 million, and $1,241 million for the preclinical period, the clinical period, and in total, respectively. Adjusting previously published estimates of R&D costs for traditional pharmaceutical firms by using past growth rates for pharmaceutical company costs to correspond to the more recent period to which our biopharmaceutical data apply, we found that total out-of-pocket cost per approved biopharmaceutical was somewhat lower than for the pharmaceutical company data ($559 million vs. $672 million). However, estimated total capitalized cost per approved new molecule was nearly the same for biopharmaceuticals as for the adjusted pharmaceutical company data ($1,241 million versus $1,318 million). The results should be viewed with some caution for now given a limited number of biopharmaceutical molecules with data on cash outlays, different therapeutic class distributions for biopharmaceuticals and for pharmaceutical company drugs, and uncertainty about whether recent growth rates in pharmaceutical company costs are different from immediate past growth rates.

I. INTRODUCTION

The financial viability of new drug and biopharmaceutical development depends on the expected costs of, as well as the returns to, R&D. When R&D costs are substantial it is important to examine approaches that could reduce those costs. If the productivity of new drug development can be improved, then more innovations may be pursued and eventually reach the patient. The Food and Drug Administration (FDA), through its Critical Path Initiative, has initiated a process to, in part, explore how the agency, industry, and academia can establish methods that would lower development costs (FDA, 2004).

R&D costs for new drugs (including the costs of failures and time costs) have been estimated to average in excess of $800 million (in year 2000 dollars) for development that led to approvals in the 1990s, with a marked upward trend relative to earlier decades (DiMasi et al., 2003). These R&D cost estimates have used data on new drugs developed by traditional pharmaceutical firms (primarily new chemical entities). No study to date has focused on the types of molecules that are developed by biotech firms. One might conjecture that biopharmaceuticals are less costly to develop because biotech firms need to be more nimble and creative or that fewer safety issues arise for many biopharmaceuticals because they replace substances that exist naturally in the body. However, some industry insiders estimate that costs, even for biotech firms, exceed $1 billion.[1]

In this paper, we make a first attempt to examine the magnitude of R&D costs associated with developing the types of molecules on which biotech firms focus. Specifically, we use drug-specific cost, development time, and clinical success rate data for therapeutic biopharmaceuticals

[1] Gottschalk (2004) notes that a manager at a biotech company estimated that his company spends in excess of one billion dollars to get a drug to market (lecture to Professor Fiona Murray's MIT Sloan Management class 15.968, "Building a Biomedical Business," by Bill Anderson, VP Business Planning, Biogen Idec, Inc., December 3, 2003).

to estimate pre-tax R&D resource costs. We then compare these results to those obtained for development of new drugs by traditional pharmaceutical firms (DiMasi et al., 2003). Given that the biopharmaceutical data are, on average, more recent than the data used for DiMasi et al. (2003), we estimate the difference in study periods. Our results for biopharmaceutical development are then also compared to those for traditional pharmaceutical firms with costs extrapolated using estimated past growth rates for pharma costs to coincide with the more recent biopharmaceutical study period.

The rest of this paper is organized as follows. Section II contains a description of the data used for our analyses. Section III describes the methods used to obtain our results. Section IV presents our results. Finally, section V summarizes our conclusions and offers some discussion of the results.

II. DATA

Our data on project costs derive from two sources. First, the sample for our study of pharmaceutical R&D costs (DiMasi, 2003) contained a small number of biologic compounds developed by pharmaceutical firms. Second, we obtained project-level and aggregate annual expenditure data for a consulting project for a biotech firm.[2] We combined data by period and type of compound from these two sources. We focus on therapeutic recombinant proteins and monoclonal antibodies (mAbs), which are overwhelmingly the two most prevalent compound types in the biotech sector. The consulting project focused on compounds that first entered clinical testing from 1990 to 2003. With compound type and period of initial clinical testing as

[2] The firm provided data on its R&D expenditures in the form required to apply the basic methodology used in DiMasi et al. (2003). The purpose was to test their hypothesis that their R&D costs were in fact significantly lower than the estimate in DiMasi et al. (2003) for traditional pharmaceutical firms.

study criteria, we utilized data on four biologics from three companies used in the earlier study and 13 compounds from the biotech firm.[3]

While the data on cash outlays are limited to the 17 compounds noted above, we are able to use a much larger dataset to estimate average development times, clinical success rates, and phase transition probabilities. These data are used to account for time costs and the costs of development failures.[4] We used a Tufts Center for the Study of Drug Development (CSDD) database of biopharmaceutical compounds. The Tufts CSDD database is constructed from information contained in a number of commercial business intelligence databases (*PharmaProjects*, *R&D Focus*, and *iDdb3*), trade press accounts, company reports and websites, and company surveys. For our analyses of development times, clinical success rates, and phase transition probabilities, we used a subset of this database. The compounds included are therapeutic recombinant proteins and mAbs that were first tested in humans from 1990 through 2003. There are 522 such compounds, and they include molecules that were abandoned during

[3] The sample consisted of nine recombinant proteins and eight mAbs.

[4] Given that we use development times and success rates for what is essentially the universe of biopharmaceuticals developed by all firms, it is not possible to infer what costs per approved new molecule are for the biotech firm that provided molecule-specific cash outlays to us. Company-specific success rates, in particular, can have a substantial impact on total R&D costs for a given company. One might wonder, however, about the internal consistency of all of the data. It is unlikely that company-specific mean clinical phase expenditures will have an appreciable effect on success rates. It is also likely that mean clinical phase costs for an investigational molecule of a given type and therapeutic class will not vary much across firms. One potential concern, though, is the possibility that there were some time-cost tradeoffs for the phase data (Scherer, 1966). This is more of a concern for molecules that fail in testing than for those that succeed, since the total amount of testing for molecules that are eventually approved for marketing is likely to be essentially the same, regardless of whether some testing is done in parallel rather than sequentially. We have no reason to believe that the biotech firm in question here differed from other firms with regard to time-cost tradeoffs.

development, as well as those that have attained U.S. Food and Drug Administration (FDA) approval.[5]

We compare our results for biopharmaceuticals to our previously developed estimates of R&D costs for new drugs developed by traditional pharmaceutical firms. The data underlying the "pharma" results are described in DiMasi et al. (2003). These data included cash outlays for 68 new drugs and development times, clinical approval success rates, and transition probabilities for a larger dataset of 534 new drugs.

III. METHODS

The methodology used for the analysis here is explained in detail in DiMasi et al. (2003). We shall only briefly outline the methods here.

1. Out-of-Pocket Costs: Phase Means, Success Rates, and Expected Costs

We refer to actual cash outlays of the firm as out-of-pocket costs. We converted the data on clinical period expenditures by phase and year to 2005 dollars using the GDP Implicit Price Deflator. We determined mean costs for these molecules for phase I, phase II, and phase III. Long-term animal testing costs incurred during clinical development, regulatory approval submission costs, and chemistry, manufacturing and control costs related to development and incurred during clinical development are subsumed in the cost estimates for the clinical phases. The expenditures considered in this report for the sample of 17 molecules are only those that were incurred prior to original marketing approval.

To obtain a full R&D cost estimate that would account for the costs of failures and the time cost of new pharmaceutical development, we must build up to one through analyses of the

[5] This dataset consisted of 278 recombinant proteins and 244 mAbs.

expected costs for the clinical and preclinical periods. For purposes of this study, by the clinical period we mean the time from initial human testing of a compound to original marketing approval. The preclinical period refers to activities engaged in prior to the start of human testing. Thus preclinical R&D costs include expenditures for both basic research and preclinical development.

Expected costs take into account the fact that not all compounds will progress all the way through development to approval. We first work at the investigational molecule level. For the clinical period this means that we must estimate the probabilities that a compound that enters the clinical testing pipeline will make it to each phase. These values can be estimated from the data in the Tufts CSDD database of biopharmaceutical compounds. Statistical inference using, in part, survival analysis to account for censoring of the data has been implemented in a number of studies of drug industry success rates.[6] However, given lengthy drug development times, such an approach requires that there be a substantial period of time between the when the most recent drug enters clinical testing and when the analysis is conducted. Since we must include here drugs that have entered the clinical testing pipeline relatively recently, we have estimated success and phase attrition rates in a more mechanistic manner. We estimated a phase transition probability to be the percentage of drugs in the sample that have proceeded from one phase to another among the set of drugs that entered the first phase and either proceeded to the next phase or were terminated in the first phase. This approach should provide reasonable estimates of phase transition probabilities since the lengths of individual phases are short relative to total development times. The implicit assumption needed for such an approach is that those drugs that are still active at the time of analysis will proceed to later phases more or less in accordance with

[6] See, for example, DiMasi et al., (1991), DiMasi (1995), Gosse et al., (1996), DiMasi (2001), DiMasi, et al., (2003).

the estimated transition probabilities. The overall clinical success rate is then determined as the product of the phase transition probabilities. Clinical success is defined as U.S. regulatory approval for marketing.

Expected out-of-pocket cost per investigational drug is the weighted average of mean phase costs, where the weights are the estimated probabilities that an investigational molecule will enter a given phase. Finally, the out-of-pocket cost per approved new molecule is obtained by dividing the out-of-pocket cost per investigational molecule by the estimated clinical approval success rate.

Preclinical costs are obtained in a manner similar to the method we used in DiMasi et al. (2003). We examined time series data on aggregate preclinical and clinical expenditures for new molecules at the firm level. These data, along with our estimated clinical period costs per investigational and per approved molecule, were used to infer the corresponding values for preclinical costs. The time series data on preclinical and clinical expenditures were linked, as was done in DiMasi et al. (2003), via an estimated 5-year lag between the middle of the preclinical period and the middle of the clinical period.[7]

2. Capitalized Costs: Development times and Discount Rate

Drug development is a very lengthy process. As such, there are substantial time costs to investing in R&D years before any potential returns can be earned. We capture the time costs of drug development in a single monetary measure by capitalizing costs forward to the point of original marketing approval at an appropriate discount rate. The discount rate used is a cost of capital estimate for a sample of firms obtained from applying the Capital Asset Pricing Model

[7] In the absence of precise data on the length of the preclinical period for these molecules, we used the value estimated for DiMasi et al. (2003). Managers at the biotech firm from which we obtained cost data agreed that the estimate was reasonable.

(CAPM). More detail on this process is explained below in the context of a discussion of the result we obtained for a biotech discount rate.

Capitalized costs are the sum of out-of-pocket and time costs. To obtain time costs we not only need an appropriate discount rate, but also a timeline over which out-of-pocket costs are capitalized forward to marketing approval at the discount rate. Thus, we estimate average clinical phase and regulatory review lengths from the data in our subset of therapeutic recombinant proteins and mAbs. As noted above, we use the estimate in DiMasi et al. (2003) for the time from discovery to first human testing.

IV. RESULTS

Our focus is on biopharmaceutical development, but we will also make some comparisons to estimated costs for traditional pharmaceutical firms.

1. Clinical Phase Costs per Investigational Molecule

Table 1 shows our estimated average clinical period phase costs for the sample of compounds for which we obtained detailed data. Mean clinical phase costs are higher than those that we had obtained in our R&D cost study for traditional pharmaceutical firms when adjusted for inflation. For the period we analyzed, the sum of the clinical period mean phase costs for biopharmaceuticals ($166 million) is 14% higher than what we had found for pharma development ($146 million).[8]

1a. Success Rate and Phase Transition Probabilities

Using information from the Tufts CSDD biopharmaceutical database, we estimated the phase transition probabilities shown in Figure 1. For comparative purpose, we also reproduce

[8] See, however, our discussion below about differences in time periods between our previous study and the data used for this report.

the phase transition probabilities for the DiMasi et al. (2003) study. Multiplying the phase transition probability estimates for biopharmaceuticals yields an overall clinical approval success rate of 30.2% (as opposed to 21.5% for pharma). To obtain an estimate of the expected clinical period cost per investigational molecule we need estimated probabilities that a molecule that enters clinical testing will reach a given phase. Those values can be derived from the transition probabilities and the overall clinical approval success rate. To be conservative, we assume a 100% success rate for regulatory approval submissions to the FDA so that the probability that a regulatory submission will be made is assumed to be the same as the overall clinical approval success rate. Previous studies have shown 100% success rates for regulatory submissions for biopharmaceuticals for almost every period analyzed (Reichert [2003, 2005]). Altering this value within reason does not have an appreciable effect on the results. Applying the probabilities as weights for the mean costs yields an estimated out-of-pocket cost per investigational molecule of $169 million for biopharmaceuticals.

1b. Out-of-Pocket Clinical Cost per Approved Molecule

What we are mainly interested in are costs per approved new molecule. We obtain such values by dividing costs per investigational molecule by the estimated clinical approval success rate (30.2%). This yields an estimate of the out-of-pocket clinical period cost per approved new molecule of $361 million for biopharmaceuticals.

2. Out-of-Pocket Preclinical Cost per Investigational Molecule

Preclinical cost per investigational molecule is obtained by multiplying our estimated clinical phase cost per investigational molecule by a ratio of preclinical to clinical expenditures obtained by applying the lag noted above to the aggregate expenditure time series data. The aggregate data, with a lag imposed, implies that clinical period phase costs should account for

65% of total out-of-pocket cost. These estimates yield an out-of-pocket preclinical cost per investigational molecule of $59.9 million, and, using a 30.2% clinical approval success rate, a preclinical out of-pocket cost per approved new molecule of $198 million.

3. Capitalized Costs

As noted above, to obtain estimates that include the time costs of new drug development we need to estimate development times and choose an appropriate discount rate.

3a. Development Times

Our data on biopharmaceutical compound development histories for the period analyzed yielded the mean clinical development and approval phase lengths shown in Figure 2. The phase results are averages across all compounds that completed the phase, regardless of whether the compound was ultimately approved for marketing. For comparative purposes we also show the pharma development time results from DiMasi et al. (2003). Total clinical plus approval time is 8% longer for the biopharmaceuticals, with nearly all of the difference accounted for by phase I.

3b. Cost of Capital

In our prior analysis of traditional pharmaceutical firms, we utilized a cost of capital of 11% as a discount rate for R&D activities that were first taken into clinical trials between 1983 and 1994 (DiMasi, et al., 2003, Grabowski, et al., 2002). This cost of capital estimate was based on concepts from modern finance theory.

Utilizing the CAPM framework (Brealey and Myers, 2000), the firm's cost of capital, r^*, is a weighted average of its cost of capital on its debt and equity capital.[9] Given the low debt

[9] The weighted average company cost of capital can be expressed in terms of the following equation:

$$r^* = r_D(1-T_C)(D/V) + r_E(E/V)$$

Where r_D and r_E are the expected rates of return on assets of comparable riskiness for the firm's debt and equity securities respectively. T_C is the firm's corporate tax rate,

values of large pharmaceutical firms, the equity cost of capital becomes the key factor driving the weighted cost of capital for the firms. In the case of biotech firms the debt component is negligible, given that long-term debt after 1990 is less than 1% of market valuation. Thus, for all practical purposes the equity cost of capital for biotech firms is the same as their weighted cost of capital.

In the CAPM framework, investors require a risk premium for holding equity in a particular company. This premium is based on the relative riskiness to investors of that company's assets. The formal measure of relative riskiness is the beta coefficient, or the firm's contribution to the variance in the returns from a diversified portfolio of equity shares. The CAPM assumes that investors hold well-diversified portfolios.

The CAPM implies that the expected return on a firm's assets (the equity cost of capital) is equal to the risk-free rate plus a risk premium which is positively related to the riskiness of the firm's assets relative to other stock market assets:

$$r_E = r_f + beta(r_m - r_f)$$

In this equation r_f is the risk-free rate (the return in treasury bonds minus a horizon premium is typically used as a proxy for the risk-free rate); r_m is the long–term rate of return for a market basket of common stock (usually the S&P index); $(r_m - r_f)$ is the equity premium, and beta is a measure of the relative riskiness of a specific firm (based on a regression analysis that yields the covariance of returns with the overall S&P index).

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and D/V and E/V are the proportion of the firm's market valuation represented by debt and equity securities respectively.

The debt component of the cost of capital is multiplied by $(1 - T_C)$, because interest on debt obligations is tax deductible, while earnings on equity shares are not.

Under CAPM, a firm with a beta of one would have the same riskiness as the overall S&P index, whereas those with values greater than one are more risky, and correspondingly, those with betas below one are less risky. Company specific values for beta can be found in Value Line's Investment Surveys and other security analyst publications. Betas in these sources are typically updated on a periodic basis.

Myers and Shyam-Sunder (1995) examined the cost of capital for seven smaller biotechnology and specialty pharmaceutical firms for 1989. These firms had higher betas and costs of capital than the major pharmaceutical firms. The greater betas or riskiness exhibited by these firms were consistent with the fact that the smaller biotech firms had fewer commercialized products and proportionately more earlier-stage R&D projects. The average cost of capital for the full sample of seven biotech and specialty pharma firms was 19% in nominal terms and 14% in real terms.

Using the same methodology as employed by Myers and Shyam-Sunder (1995) and other financial economists, we estimated cost of capital values for a sample of biotech firms at roughly five year intervals from their 1989 estimate. The lower value in 2004 reflects declining value in the risk free rate and the equity premium in recent years compared to the 1994-1999 period. The focus of our analysis is on R&D projects initiated since the mid 1990s through the early 2000s where a 10% to 12.5% rate was observed. We therefore use the average of the three values for the cost of capital in Table 2, 11.5%, as the benchmark value for biopharmaceuticals. We also perform simulations around this baseline value to analyze the sensitivity of the capitalized R&D cost to this cost of capital value.[10]

[10] Financial economists suggest that the risk and cost of capital of an individual R&D project will depend on the stage of the project and, correspondingly, on the amount and timing of follow-on investments required to achieve commercial success. By contrast, the estimates derived from corporate financial data by Myers and Shyam (1995) and other financial economists represent an average cost of capital for a firm's aggregate portfolio of R&D projects as well as their complementary capital investments in manufacturing and marketing assets. Some analyses of the pharmaceutical industry have utilized a higher cost of capital for earlier stage R&D projects based on cost of capital estimates from firms at different stages of the life cycle. For example, the Office of Technology Assessment (U.S. Congress, Office of Technology Assessment, 1993)

Discussions with a few of the leading pharmaceutical firms suggest that a nominal cost of capital in the range of 12% to 15% was being utilized by many large pharma firms in 2001-2002. (Grabowski, et al., 2002) Given a 3% rate of inflation, this would imply a 10% to 12% real cost of capital for major pharmaceutical firms. This is roughly consistent with estimates of the cost of capital derived from the CAPM in this period.

3c. Capitalized Costs per Investigational Molecule

We obtain capitalized costs by spreading our estimated expected out-of-pocket phase costs per investigational molecule over estimated mean phase lengths and then capitalizing them forward to marketing approval at an 11.5% discount rate using a representative time profile. The results are shown in Table 3.

Preclinical capitalized cost per investigational molecule is obtained by spreading the out-of-pocket cost per investigational molecule determined above ($60 million) over an estimated preclinical period (52.0 months) and then capitalizing forward to marketing approval at an 11.5% discount rate over the representative time profile. Doing so yields a capitalized preclinical period cost per investigational molecule of approximately $186 million. Capitalized clinical cost per investigational molecule is obtained by capitalizing out-of-pocket clinical phase cost forward to marketing approval according to the time profile in Figure 2. This yields a capitalized clinical period cost per investigational molecule of approximately $189 million.

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utilized a 14.5% real cost of capital for the earlier pre-clinical stages of pharma R&D based on the Myers and Shyam (1995) biotech and small firm sample, and lower values for later stages of the life cycle. Myers and Howe (1997) generate a "stair-stepped" cost of capital using a Monte Carlo simulation model and an option value approach. To our knowledge, none of the big pharma firms use a stair-stepped cost of capital in their cost and return calculations, but some are considering this approach.

4. Total R&D Costs per Approved Molecule

To get estimates of fully allocated total cost per approved new molecule, we need only add estimates of cost per approved molecule for the preclinical and clinical periods. Applying the clinical approval success rate of 30.2% for biopharmaceuticals to the capitalized preclinical cost per investigational molecule noted above yields a preclinical period cost per approved new molecule of $615 million. Similarly, applying the success rate to our estimate of capitalized clinical period cost per investigational molecule yields a capitalized clinical period cost per approved molecule of $626 million. Total capitalized cost per approved molecule for biopharmaceuticals is then $1,241 million. Out-of-pocket, time, and capitalized costs per approved new molecule are shown in Figure 3.

4a. R&D Cost Comparisons: Biotech and Pharma

Our estimates for biopharmaceutical out-of-pocket preclinical, clinical, and total out-of-pocket R&D costs are shown in Figure 4. For comparative purposes, we also show the corresponding figures for pharma from our most recent study of R&D costs for traditional pharmaceutical firms (DiMasi et al., 2003). The overall figures for pharma firms are significantly lower than those for biotech development. Biopharmaceutical costs are 46% higher for the preclinical period, 14% higher for the clinical period, and 24% higher in total.

It may be the case, however, that the appropriate figures for R&D costs for traditional pharmaceutical firms to compare with our biotech estimates should be much higher than those shown by the middle bars of Figure 4. The reason is that the biotech data are somewhat more recent than the data used for DiMasi et al. (2003). We conducted two types of comparisons to judge the extent to which the period is shifted. Examining both actual approval dates for biotech compounds in the Tufts CSDD database and for those used in the DiMasi et al. (2003) sample, as

well as average approval dates on which phase I testing began for biopharmaceutical compounds and for the data in DiMasi et al. (2003), suggested a shift of approximately five years in the study periods. Thus, we should consider what new drug development costs for pharma firms would be five more years into the future. In DiMasi et al. (2003) we compared costs for the current sample to those for an earlier period covered by a previous study (with more than a decade difference in time). We applied the growth rates (over and above inflation) for the preclinical and clinical periods that we observed between our two earlier studies on pharma costs to the most recent pharma data assuming a further five-year shift. The results are the pharma time-adjusted values given by the third set of bars in Figure 4. The unadjusted figures can be viewed as what the outcomes for pharmaceutical firms would be if they had kept cost increases in the later five-year period in line with general inflation.

The time-adjusted out-of-pocket biotech costs for the preclinical period are still somewhat higher than for pharma even with the period adjustment (32% higher). However, for the clinical period and in total, biopharmaceutical out-of-pocket costs are lower than our reported pharma costs adjusted for a later period. Specifically, clinical period costs are 31% lower and total costs are 17% lower for biopharmaceuticals. Of course, we do not know if pharma costs continued to increase at the same rates as they had in the past.

Our main results for capitalized costs are shown in Figure 5. Capitalization increases biopharmaceutical costs relative to pharma costs because of a longer development timeline and a higher cost of capital.[11] As a result, the capitalized preclinical costs for biotech are proportionately higher (40%) relative to time-adjusted pharma costs than are out-of-pocket costs.

[11] The discount rate has a modest effect on total capitalized costs. If we use a 10.5% discount rate for biotech, then its total capitalized cost falls by 6.8%. If we use a 12.5% discount rate for biotech, then total capitalized cost is 7.3% higher.

However, capitalized clinical period and total costs are proportionately closer to pharma costs than are out-of-pocket costs. Capitalized clinical period costs for biopharmaceuticals are 29% lower than for time-adjusted pharma costs. However, total capitalized cost per approved biopharmaceutical ($1,241 million) is only 6% lower than total capitalized time-adjusted pharma cost ($1,318 million).

V. CONCLUSIONS

While estimates of the level of, and trends in, R&D costs for traditional pharmaceutical firms have been published, to date no studies have focused specifically on biotech firms or particular types of biopharmaceutical development. We have taken a first step toward getting a sense for the magnitude of what the full R&D resource costs associated with discovering and developing biopharmaceuticals to the point of initial regulatory marketing approval had been for recent years. Using compound-specific costs for a sample of 17 investigational biopharmaceuticals from four firms, a time series of annual preclinical and clinical expenditures for a biotech firm, estimated average development times and phase transition probabilities for over 500 therapeutic recombinant proteins and mAbs, we estimated average preclinical period, clinical period, and total costs per approved new biopharmaceutical. We found out of-pocket (cash outlay) cost estimates of $198 million, $361 million, and $559 million per approved new biopharmaceutical for the preclinical period, the clinical period, and in total, respectively (in year 2005 dollars). These figures include the costs of compound failures. Adding time costs to cash outlays, we found cost estimates of $615 million, $626 million, and $1,241 million per approved new biopharmaceutical for the preclinical period, the clinical period, and in total, respectively (in year 2005 dollars).

Our estimates for biopharmaceuticals are higher than those we found for our previous study of pharma costs (DiMasi et al., 2003). However, the biopharmaceutical data that we used is of a more recent vintage. If past growth rates in R&D costs for traditional pharmaceutical firms are applied to the results in DiMasi et al. (2003), then total capitalized biopharmaceutical cost per approved new molecule appears to be essentially the same as estimated total capitalized per approved new drug for traditional pharmaceutical firms. However, total out- of-pocket costs for biopharmaceuticals were found to be somewhat lower, both out-of-pocket and capitalized clinical period costs for biopharmaceuticals were lower, and preclinical period costs for biopharmaceuticals were somewhat higher.[12] Determining what the actual growth rates in costs for pharma firms had been in recent years awaits further study.

Several caveats to our results should be mentioned. The results are preliminary in that the sample size for mean phase costs is relatively small, although the sample sizes for development times and success rates are quite large. Beyond this, the comparisons with pharma costs should be viewed with some caution for two reasons. First, as noted, pharma costs may not have changed to the same degree in recent years as they did in the past. Second, costs can vary by therapeutic class (DiMasi et al., 2004). The distributions of investigational compounds by therapeutic class for traditional pharmaceutical firms do differ from the distributions by class for the recombinant protein and mAb biopharmaceuticals that we examined. Specifically, investigational biopharmaceutical molecules were more concentrated in the oncology and immunologic categories than were pharma molecules for the period analyzed in DiMasi et al. (2003), while the pharma distribution was more concentrated in the cardiovascular and neuropharmacologic classes. It is unclear how these differences affect the comparative results;

[12] The higher preclinical expenditures per approved biopharmaceutical may, to some extent, help explain the higher clinical approval success rates for biopharmaceuticals.

while full clinical period costs for new cardiovascular and neuropharmacologic drugs were found in DiMasi et al. (2004) to be about average for pharma development, not enough information was available to determine costs for oncology and immunologic drugs. Additional research is needed to fully resolve these issues.

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Table 1. Out-of-pocket preclinical and clinical period cost per investigational biopharmaceutical compound (in millions of 2005 dollars).[a]

Testing Phase	Mean cost	Probability of entering phase	Expected cost
Preclinical	$59.88	100%	$59.88
Phase I	$32.28	100%	$32.28
Phase II	$37.69	83.7%	$31.55
Phase III	$96.09	47.1%	$45.26
Total			$168.97

[a] All costs were deflated using the GDP Implicit Price Deflator.

Table 2. Nominal and Real Cost of Capital (COC), 1994 – 2004

	1994	2000	2004
Nominal COC (%)	17.0	15.0	13.0
Inflation rate (%)	4.5	3.0	3.0
Real COC (%)	12.5	12.0	10.0

Table 3. Capitalized preclinical and clinical period costs per investigational biopharmaceutical compound (in millions of 2005 dollars).[a]

Testing Phase	Expected Out-of-Pocket Cost	Phase length (mos.)	Monthly Cost	Start of phase to approval (mos.)	End of phase to approval (mos.)	Expected capitalized cost[b]
Preclinical	$59.88	52.0	$1.15	149.7	97.7	$185.62
Phase 1	$32.28	19.5	$1.66	97.7	78.2	$71.78
Phase II	$31.55	29.3	$1.08	78.2	48.9	$56.32
Phase III	$45.26	32.9	$1.38	48.9	16.0	$60.98
Total						$374.70

[a] All costs were deflated using the GDP Implicit Price Deflator.
[b] Expenditures capitalized forward to the point of marketing approval for a representative time profile at an 11.5% real discount rate. The estimated length of the approval phase is 16.0 months.

Figure 1. Transition Probabilities for Clinical Phases

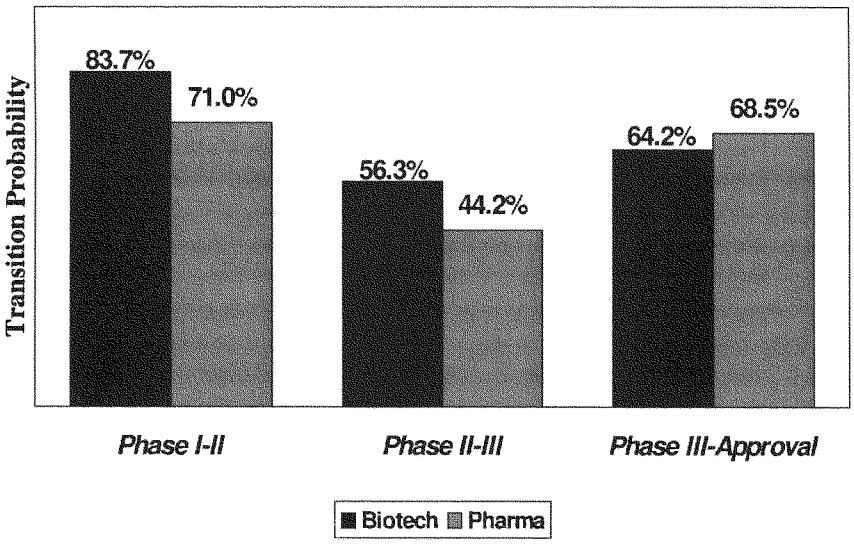


Figure 2. Clinical Development and Approval Times

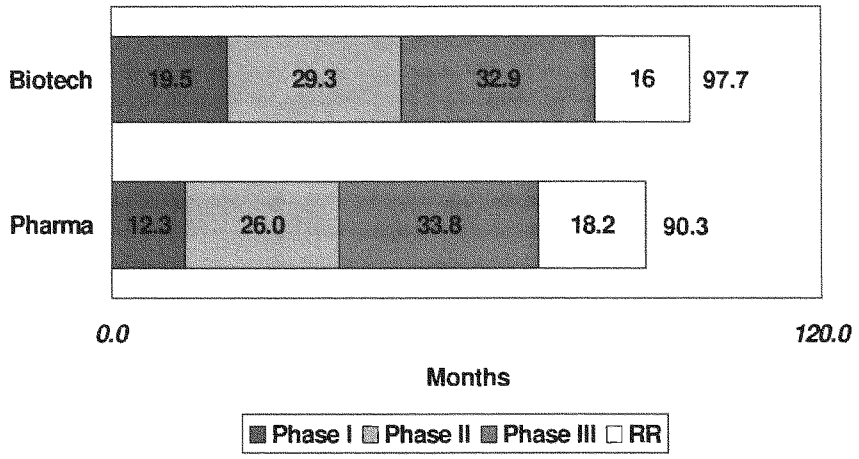
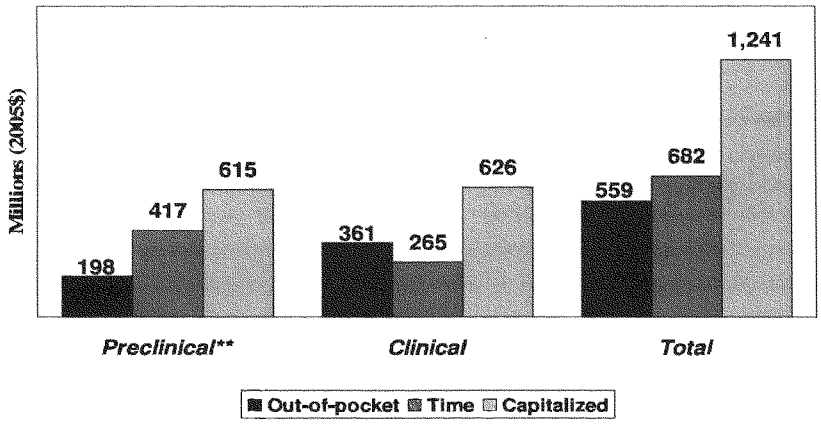
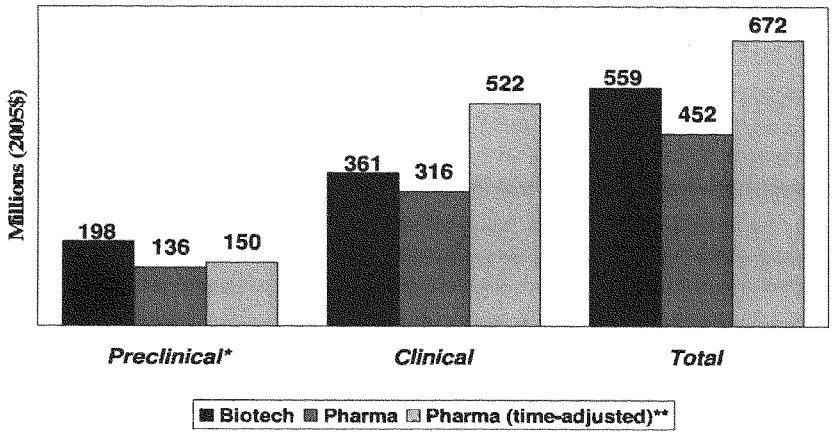


Figure 3. Pre-Approval Out-of-Pocket (cash outlay) and Time Costs per Approved New Biopharmaceutical*



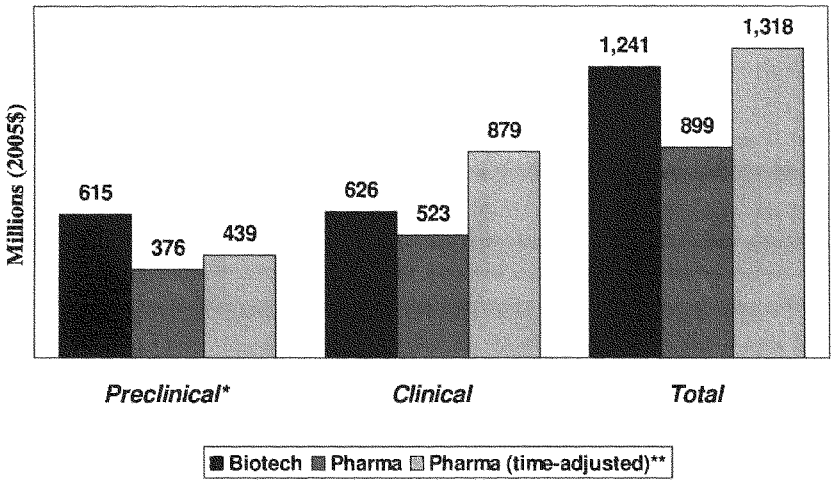
* Based on a 30.2% clinical approval success rate
** All R&D costs (basic research and preclinical development) prior to initiation of clinical testing

Figure 4. Pre-Approval Cash Outlays (out-of-pocket cost) per Approved New Molecule



* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing
** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

Figure 5. Pre-Approval Capitalized Cost per Approved New Molecule



* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing
** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

Chairman WAXMAN. Thank you very much, Dr. Grabowski.
Mr. Houts.

STATEMENT OF JONAH HOUTS

Mr. HOUTS. Good afternoon, Chairman Waxman and fellow committee members. My name is Jonah Houts. I am a senior analyst with Express Scripts. 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 for his leadership in introducing this legislation, which we believe will fundamentally improve health outcomes by giving patients access to lower-cost biological alternatives.

Express Scripts monitors prescription drug trends and expenditures for 1,600 clients, including large self-insured employers, government payers, unions, and health insurance companies. I would like to talk about three basic issues today. First, I would like to speak about the trend of specialty drug spending, especially biologic agents. Second, I would like to describe the tools used by the PBM industry to control the increase in cost of prescription drugs. Third, I would like to describe how we would apply these tools to biogenerics and the potential benefit to patients, plan sponsors, and the Government.

Spending on pharmaceuticals now represents 11 percent of total health care spending. Within the pharmaceuticals are specialty drugs. These are the most high-priced biologic agents, which we are discussing here today.

I brought an exhibit which may demonstrate the increased growth here. In 2006, spending on specialty drugs was $54 billion, representing 20 percent of pharmaceutical spending. The rate for specialty drugs will almost double by 2010 to $99 billion. This rate of increase is the second highest in all of the health care field, exceeded only by diagnostic imaging tests.

In total, Express Scripts manages the pharmacy benefit for over 50 million individuals in this country. Our mission is to make the use of prescription drugs safer and more affordable. To this end, we have developed sophisticated tools, such as formularies, tiered copayments, step therapies, and 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 that we have is the promotion of generic medications. These therapies are time tested and thus are clinically effective. They also have well characterized safety profiles. The additional advantage is that they are the most affordable for both patients and plan sponsors. For these reasons, patients achieve higher compliance rates with these therapies. Utilizing programs like I previously described, our company has an industry leading generic fill rate of 60 percent.

But 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 committee is made up of both specialty and general medicine doctors, and pharmacists who are not employees of Express Scripts. Safety has and always will be of primary concern to Express Scripts.

As we have stated, spending on biologic agents is increasing at an alarming rate. This legislation will allow for a pathway at the FDA for companies to bring to market generic versions of these important medications.

The PBMs have the tools to assist patients in switching to the most cost-effective biogenerics. In fact, our switching tools will be even more effective in this market because of the limited number of patients, the limited number of prescriptions, the limited prescribing community, and the potential for enormous savings. Our plan sponsors will be very motivated to have us pursue each and every savings opportunity.

We are pleased to hear the FDA today not rule out interchangeability in the future, but, regardless, if the FDA deems a product is interchangeable or just comparable, will be quite effective at working with the prescribing physician to aid patients in receiving the most cost-effective and clinically appropriate therapy.

In the realm of branded pharmaceuticals, drugs compete on their research and development and marketing. It would be irrational for branded drugs to compete on price, as they are competing within a finite group of patients, and price reductions would result in reduced revenues for all manufacturers in the class. Generic drugs, however, can only compete on price. Without this extensive research and development, the only way for a generic to capture market share is on price. This price competition benefits payers, plans, and the Government.

This historic legislation would allow patients, payers, physicians, and PBMs to work together to make these wonderful therapies more available, with improved health outcomes and tremendous savings.

[The prepared statement of Mr. Houts follows:]

TESTIMONY OF JONAH HOUTS
SENIOR ANALYST, EXPRESS SCRIPTS, INC.

BEFORE THE
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM
U.S. HOUSE OF REPRESENTATIVES

HEARING ON
SAFE AND AFFORDABLE BIOTECH DRUGS:
THE NEED FOR A GENERIC PATHWAY

March 26, 2007

Good Morning Chairman Waxman, Ranking Member Davis and Members of the Committee.

I am Jonah Houts, Senior Analyst 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 for his leadership in introducing this historical legislation which we believe will fundamentally improve health outcomes by giving patients access to lower-cost biologic alternatives.

Express Scripts monitors prescription drug trends and expenditures for 1600 clients including large, self-insured employers, government payers, unions and health insurance companies.

I want to talk about three basic issues today:

- First, I want to talk about the trend of specialty drug spend, especially biologic agents.
- Second, I would like to describe the tools utilized by Pharmacy Benefit Managers to control the increasing cost of prescription drugs.
- Third, I want to describe 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% of total health care spend. Within the pharmaceuticals are specialty drugs, which are mostly the high priced biologic agents being discussed today. In 2006, spending on specialty drugs was $54 billion, representing 20% of the pharmaceutical spend. The spend for specialty drugs will almost double by 2010, increasing to $99 billion. This rate of increase is the second highest in the health care field, exceeded only by diagnostic imaging tests.

II. Tools of the PBM

Express Scripts represents 1600 clients, including employers, unions, governments, and managed health plans. In total, we are managing the pharmacy benefit for over 50 million individuals. Our mission is to make the use of prescription drugs safer and more affordable. 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, and thus are clinically effective, and have well characterized safety profiles. The additional advantage is that they are the most affordable for patients and plan sponsors. For these reasons, patients achieve higher compliance rates with these therapies. Utilizing these programs, our company has an industry leading generic fill rate of 60%.

When a particular drug comes off patent and can be filled with a generic, that fill rate climbs to 96%. 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 of anti-convulsant drugs, what we call a narrow therapeutic index, physician prescribing patterns are more cautious and we see a generic fill rate of 83%.

These switch 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 committee is made up of both specialty and general medicine doctors and pharmacists who are not employees of Express Scripts.

III. How We Would Apply These Tools to Biogenerics

As we have stated, spend on biologic agents is increasing at an alarming rate. This legislation will establish a pathway at the FDA for companies to bring to market generic versions of these important medications. The PBMs have the tools to assist patients in switching to the more cost effective biogenerics. In fact, our switching tools will be even more effective in this market because of the limited number of patients, scripts, specialty physicians and the potential enormous savings. Our plan sponsors will be very motivated to have us pursue each and every savings opportunity.

Regardless if 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 receiving 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. ESI concluded that three statins were in the "high-potency" category.

In this case, statin A had a much higher price than statin B and we educated consumers and physicians about the lower cost alternative brand product. We successfully moved 49% 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. At that time Express Scripts moved 96% of market share to the preferred generic agent within 3 months, resulting in $126 million of savings for our clients in the area of anti-cholesterol drugs alone.

Biologics are the fastest growing segment of drug spend and there are 400 to 700 biologics in the pipeline. While they have remained a relatively small percentage of prescriptions, they account for a large portion of spend which is growing. 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% on branded oral-solid medications. The range of savings associated with the FDA's ability to approve biogeneric products remains unclear, largely because of interchangeability or comparability, but what is clear is that each study looking at this issue finds savings in the billions for the federal government.

This historic legislation will allow patients, payers, physicians and PBMs to work together to make these wonderful therapies more readily available, with improved health outcomes and tremendous savings.

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

I want to thank all of you for your testimony, especially Ms. Brown and Ms. Nathan. Your very moving testimony is what this legislation is all about. When drugs are miracles, but the miracles are too expensive for people, they are not going to be there for them, and that is why we need to figure out a way to hold down costs. Providing generics is certainly, to me, one of the best ways to hold down costs. Others have suggested other ideas, but competition, market forces I think do work and have worked in the past.

Ms. Mathur, I find it stunning that in California spending on biologics or specialty drugs in 2006 was $83.7 million, and that is at a cost of $55 per day, compared to $2 per day for traditional drugs. If those kinds of spending trends are maintained, what will be the impact on CalPERS and your members in the future?

Ms. MATHUR. I think we really are at unsustainable levels, and what we fear is that in the future we will have to shift more of the cost on to the member, either through increases in co-pays or by raising premiums. We have already heard stories from some of our members that, as the cost of health care increases overall, they are less and less able to afford health care, even through our program. I would hate to see some of our members drop health care coverage that is available to them simply because they cannot afford it.

Chairman WAXMAN. Dr. Grabowski asserts that the savings from generic competition in the biologics context will be modest, in the range of 10 to 25 percent. What would even those modest savings mean for CalPERS? And let me ask this also of Mr. McKibbin for Illinois.

Ms. MATHUR. I'm sorry, Mr. Chairman. I thought you were directing that to Mr. Grabowski.

Chairman WAXMAN. The 10 to 25 percent savings, Dr. Grabowski says those are modest.

Ms. MATHUR. Yes.

Chairman WAXMAN. What will that mean, however?

Ms. MATHUR. I think it would be extremely significant. I mean, the cost for some members, $300,000 a year, 10 to 15 percent or 10 to 25 percent is a significant savings. So even though on a percentage basis the savings for biotech drugs or biogenerics might be less than for synthetic drugs, it is certainly, on an aggregate total cost basis, going to be a very large number.

Chairman WAXMAN. Mr. McKibbin.

Mr. MCKIBBIN. For Illinois, Mr. Chairman, we are talking about $20 to $50 million, depending on when we start it, if we start it this year. And those are numbers that come out of the base, so, as you know, if this trend continues at 15 percent plus, we, too, like California, will reach this point where it is not sustainable, so we will either have to make those tough choices of trying to pass more costs or to limit access, which is untenable.

Chairman WAXMAN. Thank you.

Mr. Houts, one of the frequent assertions we hear from BIO, the trade association for the brand name biotech drugs, is that when a generic pathway for biologics is established we are not going to see much in the way of savings because generic biologics won't be interchangeable like they are with traditional generic drugs. Obviously, we might disagree on the number of biologics that will end

up being interchangeable, but assuming BIO is correct that a high number of biologics will be just comparable instead of interchangeable, what kind of impact will that have on spending on biologics?

Mr. HOUTS. There is still a significant savings opportunity, even if interchangeability is not granted by the FDA. Managed care plans and the PBMs, a recent example would be in the statin market, where there was a high-priced, effective statin, Statin A, and then a lower-priced and still effective Statin B. While they were different chemical entities, we were able to move market share to the cost-effective product.

We were actually able to move 49 percent of the market share when they weren't interchangeable, as you will. And so there is still a significant opportunity in the area of biologics to move patients to the preferred safe, effective, cost-effective products.

Chairman WAXMAN. Well, you said it would be safe. When therapeutic switches are made, what process is in place to protect patient safety?

Mr. HOUTS. All of those decisions are reviewed by our pharmacy and therapeutics committee that I referred to in my testimony, and this is composed of specialist physicians, and other physicians to ensure that drugs in those classes will have no adverse effects on patients.

Chairman WAXMAN. Thank you very much.

Mr. Danny Davis.

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman.

Once again, let me thank you for calling and conducting this hearing. It has, indeed, been informative, and I want to thank all of the witnesses for their testimony. I especially want to echo the sentiments that you expressed, Mr. Chairman, relative to the impact of the testimony of Ms. Brown and Ms. Nathan, consumers for whom all of us work. Hopefully, as a result of their experiences and their testimony, the hearing heightens the recognition that we must do something, and do it as quickly as possible, to try and make sure that we have available the very best and the most cost effective medical care that the country can provide. So I certainly want to again thank both Ms. Brown and Ms. Nathan for being here and for their testimony.

Mr. McKibbin, let me just commend the Governor for the State of Illinois. When I see the kind of interest that Rod Blagojevich has shown relative to health care, and especially the effort to try and make sure that pharmaceuticals are available to all of our residents at a cost for which they can pay, it makes me proud to live in the State of Illinois and proud to know that he is, indeed, our Governor. Please convey that to him.

Mr. MCKIBBIN. I will.

Mr. DAVIS OF ILLINOIS. If I could direct your attention to the chart located over here, which shows the five largest Medicare Part B drug expenditures in 2005—and you may not be able to see, but listed are all of the medicines listed of biotech drugs that are regulated as biologics. Spending on Epogen, an anemia treatment, alone, was over $1.7 billion, but it was actually even higher than that, because those numbers on the chart do not include spending on the end-stage renal disease, ESRD program. Three of the other drugs are also anemia treatments, and they collectively represent

over $2.1 billion in Medicare spending. Remicade, an arthritis medicine, accounted for $541 million.

My question is: are we seeing those same kind of trends in the State of Illinois? And in terms of State spending, what are the five top biologics in the State of Illinois?

[The information referred to follows:]

Biotech Drugs Dominate Medicare Spending

Five of the largest Medicare drug expenditures under the program's Part B are for biotech medicines used to treat anemia, Psoriasis, colitis, and Crohn's disease. The spending for fiscal 2005, the most recent year for which data is available, includes only drugs used in doctors' offices. The costs for drugs administered in hospital clinics or outpatient centers haven't been counted.

DRUG	MANUFACTURED BY	TREATS	FY 05 MEDICARE SPENDING
Epogen	Amgen Inc.	Anemia	$1,750,000,000
Aranesp	Amgen Inc.	Anemia	$850,000,000
Procrit	Ortho Biotech Products LP	Anemia	$776,000,000
Remincade	Centocor Inc.	Psoriasis, colitis, Crohn's disease	$521,000,000
Neulasta	Amgen Inc.	Anemia	$524,000,000

Source: CQ Weekly, October 2, 2006, www.cq.com

Mr. MCKIBBIN. Well, Congressman, we are seeing those similar type of numbers, and anyone who has a television will recognize those drugs because they are fairly heavily advertised, but those five drugs on your screen, I did a quick analysis and we are talking about $23 million a year, a little over $23 million for those five drugs on your particular chart.

For us, I took a look at the top five for just our State employee retiree group, and those top five were Enbrel, Humira, Avonex—which was talked about earlier—Lantus, and Forteo. Those were the top five drugs from a total dollar amount. On a per patient basis they are slightly different, but those five drugs are our top five, and not dissimilar to your chart. In some cases the difference may be because of Medicare and where Medicare may cover, versus an employee group, but we are seeing those similar types of trends.

Mr. DAVIS OF ILLINOIS. I know that all of us throughout the country moan and groan and talk about the speculation of Medicare and Medicaid and whether or not there are going to be increases or decreases. Many of the hospitals kind of operate on shaky ground every year. They are wondering whether or not they are going to experience severe cuts.

Are they going to have to close departments or, in some instances, actually go out of business? Should we continue to see increases in pharmaceutical drug costs, what impact do you think that would have on the hospitals, for example, in the State of Illinois, as well as throughout the Nation?

Mr. MCKIBBIN. Certainly, Congressman, it could be the tipping point, and that is something that we are very concerned about. I know yourself and others in the delegation are concerned, and we would urge that this legislation be passed sooner rather than later. As I said earlier, you know, every day that goes by is a day that is a lost opportunity, and it may be, in fact, a tipping point for hospitals in the Illinois, metro Chicago, and the rest of the United States.

Mr. DAVIS OF ILLINOIS. Mr. Chairman, I see that the light is on, but could I ask Mr. Houts if he could respond to that same question relative to the continued escalation of pharmaceutical costs without relief, how this will affect the Medicare/Medicaid programs, and certainly their impact on our hospital infrastructures?

Mr. HOUTS. It is not really a field of expertise for me as far as government payers. What I can say is that there is an exceptional opportunity for the Government in terms of Part B and end-stage renal disease, especially looking at those top drugs listed there, to save a pronounced amount of money. And so, as you consider this legislation, you may want to find ways to make Part B and the ESRD program more comparable to the commercially insured market and adopt some of the tools we use to manage trend.

Mr. DAVIS OF ILLINOIS. Well thank you very much.

Mr. Chairman, again, I just simply want to commend you for your insight in introducing this legislation, the leadership that you continue to provide. I have always known of your strong interest in health care. You probably would not remember it, but way back in a different life when I used to come to D.C. to lobby on behalf of the National Association of Community Health Centers, you were always the person that we felt that we could come to and get

some understanding. I mean, Senator Kennedy over in the Senate and Representative Waxman here in the House, you were our guys. I want to thank you again.

Chairman WAXMAN. Thank you. Now you are one of our guys, too. Thank you for your kind comments.

I very much appreciate all of our witnesses in this panel, as in the previous panels.

I would like to ask unanimous consent that all Members have 5 days to submit additional questions for the record to the witnesses that have appeared before us today.

That concludes our hearing, and our meeting is adjourned. Thank you very much.

[Whereupon, at 1:29 p.m., the committee was adjourned.]

[The prepared statement of Hon. Elijah E. Cummings and additional information submitted for the hearing record follow:]

U.S. House of Representatives
110th Congress

Opening Statement

Representative Elijah E. Cummings, D-Maryland

Full Committee Hearing:
"Safe and Affordable Biotech Drugs – The Need for a Generic Pathway"
Committee on Oversight and Government Reform

March 26, 2007

Mr. Chairman,

Thank you for holding this vitally important hearing to examine the high cost of biotech medicines to our health care system, as well as the prospects and the need for safe and affordable generics.

As you know, biotech drugs, also known as biological drugs or biopharmaceuticals, are one of the fastest growing and most expensive categories of drugs.

These drugs are often life-saving, and they encompass a broad spectrum of products, ranging from relatively easy to make human growth hormone and insulin to much more complex medicines like vaccines or blood products.

The Federal Drug Administration (FDA) has approved more than 250 biotech medicines that are on the market today. In 2005 alone, FDA approved 39 biologic products and medications.

These products serve over 800 million patients worldwide.

They are used to treat common diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.

Yet, the costs of these necessary drugs are high—and increasing.

In 2005, the five largest Medicare Part B drug expenditures were for biotech medicines regulated as biologics.

In fiscal year 2005, the single largest drug expenditure for the Centers for Medicare and Medicaid Services (CMS) was $2 billion on Epogen, a biologic for anemia.

The high cost of these medicines increasing the burden on employers, insurers, and the federal government.

We can help reduce the cost of these drugs by creating a pathway that would allow the FDA to approve safe and affordable copies, or generics, of biotech drugs.

Generics often cost 80 percent less than the brand name drug.

Chairman Waxman has been instrumental in the establishing the requirements and procedures for approving generic drugs under the 1984 "Hatch-Waxman" Act.

Under Hatch-Waxman, FDA is permitted to approve generic versions of traditional drugs on the basis of abbreviated applications.

But in 1984, the science of biotech medicines was in its infancy. As a result, the Hatch-Waxman legislative scheme focuses primarily on traditional drugs.

To be sure, the FDA has been able to approve some simpler biologics under Hatch-Waxman, on an abbreviated basis, including the human growth hormone Omnitrope.

Additionally, manufacturers of biotech drugs are permitted to make significant changes in their manufacturing processes without repeating the original clinical trials.

This further makes the case for approving generic biologics.

FDA has yet to provide guidance on generic biologics, and absent such guidance, I think that legislative action may be necessary.

I look forward to the testimonies of today's witnesses and yield back the remainder of my time.

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March 26, 2007

James C. Greenwood
President & CEO

The Honorable Henry A. Waxman, Chairman
The Honorable Thomas M. Davis, III, Ranking Member
Committee on Oversight and Government Reform
U.S. House of Representatives
2157 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Waxman and Ranking Member Davis:

The Biotechnology Industry Organization (BIO) is writing with respect to your Committee hearing on "Safe and Affordable Biotech Drugs—The Need for a Generic Pathway," to be held March 26, 2007. We respectfully request that this letter be submitted to the record for that proceeding.

We are writing to identify and describe the following key issues related to follow-on biologics: 1) our continued opposition to the "Access to Life-Saving Medicine Act" (H.R. 1038); 2) the importance of ensuring a thoughtful, deliberative process for considering the establishment of any regulatory pathway for follow-on biologics; 3) our analysis of prior studies by Pharmaceutical Care Management Association (PCMA) and Express Scripts that substantially overestimate potential savings in health care costs that might result from the establishment of a pathway for regulatory approval of follow-on biologics; and finally to 4) respond to several points raised in a Dear Colleague letter dated March 22, 2007. We will discuss each of these issues in more detail below.

First, BIO members work on the forefront of medical advancement, developing innovative biological products that have revolutionized the treatment of diseases, including cancer, heart disease, infections, arthritis, and multiple sclerosis. In order to ensure a future of continued innovation by the biotechnology industry, it is essential that Congressional deliberations about developing an approval process for follow-on biological products be driven by responsible science, with a focus on protecting patient safety and preserving incentives to ensure innovative, safe and effective biopharmaceuticals can reach patients in a timely manner. In addition to ensuring patient safety, any follow-on biologics pathway created by the Congress must preserve incentives for research and innovation by ensuring protections for intellectual property and by providing data exclusivity for innovative therapies and cures.

Unfortunately, H.R. 1038, which proposes to create such a pathway, is deeply flawed in all three respects. The bill raises numerous patient safety concerns. It would eviscerate incentives to develop life-saving new medicines through its one-sided alteration of long-standing patent law in ways that favor follow-on biologics' manufacturers, who would be

able to restrict and infringe the intellectual property rights of various parties including innovative biotechnology companies. And it lacks any data exclusivity for innovative biologics. Data exclusivity provisions have served as an incentive for innovation under Hatch-Waxman and are part of the European system for regulating "biosimilars" (i.e., follow-on biologics). But this legislation contains no prohibition on the FDA approving a follow-on product relying on innovator data immediately following approval of the reference product. Devaluing property rights and the absence of data exclusivity will reduce incentives for the investment needed for a strong, vibrant pioneer biologic industry upon which any follow-on market would wholly depend.

Second, we urge Congress to consider action relating to establishing a statutory pathway for approving follow-on biologics independent of the reauthorization of the Prescription Drug User Fee Act (PDUFA). Before a framework for follow-on biologics can be established, Congress must carefully consider and resolve complex scientific, legal, and economic issues. Meanwhile, it is important that Congress complete the PDUFA reauthorization in a timely manner. Although PDUFA formally expires on September 30, 2007, reauthorization needs to occur earlier this year to avoid potential delays in review of innovative new medicines. We believe that attaching follow-on biologics legislation to PDUFA would jeopardize reauthorization of the user fee program to the detriment of patients waiting for new therapies, FDA's internal scientific capabilities, and biomedical innovation.

Third, based on BIO's analysis of recently conducted studies relating to potential cost savings from follow-on biologics, we believe it is unlikely that follow-on biologics will produce anything close to the savings recently claimed in these studies published by PCMA and Express Scripts. These reports contain serious flaws including assumptions that raise serious questions about their validity. These flaws include:

- Assumptions about patent expirations that are inconsistent with credible analyst reports seriously call into question more than $40 billion of the alleged savings cited by the Express Scripts study;
- Calculation errors in the PCMA study result in an overestimation of savings of 40 percent, even before examining its other assumptions;
- Internally inconsistent allegations of interchangeability in the Express Scripts study call into question an additional $13.8 billion in alleged potential savings;
- Presuming that a pathway under one law would generate savings for products approved under another law calls into question over $17 billion in additional alleged savings in the Express Scripts study;
- Market penetration rates for follow-on biologics incorrectly modeled on generic drug experience are inconsistent with credible published analyses;
- Calculations based on determinations of interchangeability that include presumption of savings beginning in 2007 are unsupported in both studies.

As a result of numerous flawed assumptions and lack of any credible evidence to support these alleged savings, we believe these studies should be rejected as unreliable. In addition, a recent study from the consulting firm Avalere Health projects that federal

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health care programs would save 95% percent less over the next decade from follow-on biologics than the projected savings of $71 billion cited by Express Scripts. BIO's detailed analysis of these studies is available at: http://www.bio.org/healthcare/followon/20070222.pdf

Finally, the attachment to the Dear Colleague dated March 22, 2007, made six assertions, which BIO wishes to correct:

Assertion 1: *Under H.R. 1083, follow-on biologics "must not only be safe, pure, and potent, but also safe, pure and potent to exactly the same degree as the brand name product."*

BIO wholeheartedly agrees that this is the right standard for FDA approval of follow-on biologics—unfortunately, the proposed bill lacks any such requirement. The bill instead provides that:

> "Any person ... may submit an application under this paragraph for a biological product that differs from, or incorporates a change to, the reference product ... *including a difference in safety, purity, or potency*, so long as the application contains sufficient information to establish the safety, purity, and potency of the biological product *relative to* the reference product..." (New proposed Section 351(k)(2) of the Public Health Service Act (PHSA)) (emphases added)

Further, while the bill defines "comparability" in a way that purportedly requires the "absence of clinically meaningful differences between the two products," it adds language that ties this absence of differences to only those differences that can be detected based upon a statutorily limited pool of data: non-clinical studies, and—only if "necessary"—clinical studies that must "avoid duplicative or unethical clinical testing." Similarly, the "Dear Colleague" attachment asserts that, with respect to meeting approval standards, "if the only way to show this is to do as many, or more, studies than were done on the brand name product, the Access to Life-Saving Medicine Act authorizes FDA to require them." Again, the proposed bill does not include any language to this effect, and instead attempts to limit FDA's ability to require clinical testing. BIO also disagrees with the notion that FDA should be permitted to require these studies only if they are "the only way" to establish safety and effectiveness. BIO believes that FDA should be able to require clinical studies or trials if they are *a better way* to ensure patient safety.

Assertion 2: *"[T]he current statute gives the FDA complete discretion to decide whether clinical trials are necessary at all for the approval of a brand-name biotech drug—and in some cases has not required them."*

To the contrary, the Federal Food, Drug and Cosmetic Act (FFDCA) states that a new drug application shall include "full reports of investigations" which have been made to show whether or not such drug is safe for use and whether such drug is effective in use, and that an application shall not be approved without "adequate and well-controlled investigations, including clinical investigations" supporting the application. (FFDCA Sections 505(b)(1) and (d)). These same standards have been applied to biologics approved under the FFDCA or the PHSA. In fact, it is FDA's longstanding and

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consistent policy to require clinical trials for approval of all new drugs and biologics, and we do not know of examples of new biologics that have been or would be approved without results of clinical trials, except in those extraordinarily rare cases where it may be unethical or not feasible to conduct them (*i.e.*, with certain bioterrorism countermeasures).

Assertion 3: *H.R. 1038 "authorizes the FDA to impose exactly the same post-market study conditions on a copy of a biological product as on the brand-name product."*

To the contrary, H.R. 1038 does not impose the same post-marketing study conditions on the follow-on sponsor; in fact, the standard is narrower:

> "If the Secretary has agreed with the sponsor of the reference product that the sponsor shall conduct one or more postmarketing safety studies, the applicant *may agree* with the Secretary to conduct a similar post marketing safety study or studies *upon a reasonable showing that such study or studies would provide relevant information not available from the studies on the reference product.* The Secretary shall not, as a condition of approval, propose any additional postmarketing studies." (New proposed Section 351(k)(5) of the PHSA) (emphases added)

Rather than imposing a narrower standard for the follow-on product, BIO believes that reasonable protection of public health would, in fact, demand that the requirements be broader, given that, under this bill, a follow-on biologic that is merely comparable or even non-comparable to an innovator product could be approved for marketing utilizing an abbreviated approval process.

Assertion 4: *"Thus, using the [FDA] Comparability Protocol policy, the industry has demonstrated that, for many biotech drugs... it is possible to manufacture an interchangeable product in multiple different ways, on multiple different sites and/or using multiple different sources of raw materials."*

FDA's comparability guidance has little or no relevance to follow-on biologics. It applies to changes in an already approved product (which was approved based on a full set of investigations and data), and as to which the sponsor has full details of the manufacturing process – and thus can evaluate the potential effects of a specific, discrete change in the process. As FDA's Comparability Guidance states: "Knowledge of the process involved in the manufacture of the product is an integral component in determining the design of an appropriate comparability assessment program." The experience of a biological products manufacturer with manufacturing a particular product provides the context within which "comparability protocols"—as that term is currently used by FDA—can legitimately be used.

The follow-on manufacturer, in contrast, proposes to use a different master cell line, different manufacturing facility, and different manufacturing process, and importantly does not even know how big the differences are. In these circumstances, a "comparability" determination, as contemplated by the FDA guidance, cannot be made. Indeed, clinical trials likely would be required for changes of such a magnitude, even in situations where a manufacturer was making a different version of its own product.

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Assertion 5: *"The FDA has approved abbreviated applications (with no or limited clinical studies) for copies of these products despite the fact that the new manufacturers use different manufacturing processes than are used to make the brand name products."*

The products listed in the "Dear Colleague" attachment were all approved under Section 505 of the FFDCA, not under the PHSA, and H.R. 1038 would apply only to the latter category of biologics. Furthermore, all of them did require clinical studies prior to marketing. In the case of Omnitrope, and as FDA has made clear in public documents, Sandoz submitted extensive original clinical trial data supporting approval of Omnitrope. In fact, Sandoz submitted the results from three sequential, multicenter, phase 3 pivotal trials, and also submitted the results from a separate multicenter phase 3 clinical trial with its safety update to the application.

Assertion 6: *The U.S. should not adopt the European practice of requiring an open and transparent public process for establishing the scientific requirements for approval of follow-on biologics.*

As Europe has recognized, the scientifically complex field of follow-on biologics demands a deliberative and thorough public process by which the scientific community and relevant experts can weigh in on the appropriate requirements for approval of such products. And as European regulators also have recognized, the complexities of reviewing biosimilars require a process for establishing data requirements that is different from, and more extensive then, what would be necessary for review of innovator products. In contrast, H.R. 1083 would permit FDA and follow-on manufacturers to determine these requirements behind closed doors and without needed transparency.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. On behalf our members, we appreciate your consideration of our views and look forward to a continuing dialogue on this important topic.

Sincerely,

James C. Greenwood
President and CEO

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