

THE LAW OF BIOLOGIC MEDICINE

HEARING

BEFORE THE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

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THE LAW OF BIOLOGIC MEDICINE

WEDNESDAY, JUNE 23, 2004

UNITED STATES SENATE,
COMMITTEE ON THE JUDICIARY,
Washington, DC.

The Committee met, pursuant to notice, at 10:17 a.m., in room SD-226, Dirksen Senate Office Building, Hon. Orrin G. Hatch, Chairman of the Committee, presiding.

Present: Senators Hatch, Leahy, Durbin, and Schumer.

OPENING STATEMENT OF HON. ORRIN G. HATCH, A U.S. SENATOR FROM THE STATE OF UTAH

Chairman HATCH. Good morning. I apologize for being late. This morning has been a very hectic morning for me, so I apologize to all of you who have had to wait.

For those of you who came here for the previously scheduled judicial nominations hearing, let me just say this: Boy, are you in for a big surprise.

[Laughter.]

Chairman HATCH. I just hope it is not too dull a surprise for you and that you enjoy a good debate over the proper reach of Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act.

Today, the Judiciary Committee will consider a complex subject area that involves law, economics, science and medicine. The purpose of the hearing is simple, although the law and science surrounding these issues are not. We will explore some of the key issues concerning the legality, feasibility and advisability of creating a new, abbreviated regulatory pathway at the Food and Drug Administration for the review and approval of off-patent biological products.

First, for those of you who may not be sure what a biologic is, I would like to offer a simple working definition. Biological medicines are large, complex protein molecules derived from living cells often by recombinant DNA technology. The area of biologics is of growing medical and economic importance. The biotechnology market posted a total of about \$30 billion in sales last year, which is now expected to double to over \$60 billion by 2010.

We will see a concurrent explosion in the numbers of biologics. There are now over 150 FDA-approved products on the market, with an additional 350 in various stages of human clinical testing, and over 1,000 others in the developmental pipeline.

But more important than commercial considerations, it is the hope of many that biological products such as those that may 1 day be developed from embryonic stem cells could lead to cures to many

diseases that cannot be successfully treated today. Biopharmaceuticals appear to represent the future of medicine.

For example, now that we have mapped the structure of the human genome, we are in a position to unravel the mysteries of the function of human genes and the proteins that they encode. Nothing less than a revolution in our understanding of human health and disease is well underway. I am proud of the fact that scientists at the Huntsman Cancer Institute at the University of Utah are helping to lead the way.

The old model of large-patient-population, small-molecule medicine is giving way to large-molecule, small-patient-population therapies. The day may even come when individualized therapies will become common. These developments, of course, are not going to occur overnight, nor will they occur without great effort and ingenuity, and they will not be done on the cheap. One thing is certain. When medical breakthroughs occur, patients will want access to these new products and their families and third-party payers will want to pay as little as possible for them.

Experts remind us that this new wave of therapeutic protein molecules is more complex to discover, manufacture and use than conventional small-molecule drugs. We know that many of these new biological products tend to be more expensive than old-line, chemically-synthesized drugs. Some of these new wonder therapies cost over \$10,000 per year or per course of treatment. For example, human growth hormone can cost \$25,000 per year.

Cost factors alone compel a thorough examination and public discussion of the merits of developing a fast-track review and approval system that can reduce the price of biopharmaceuticals once patents expire. Moreover, from a regulatory reform perspective, it should always be the goal of Government to employ the least burdensome regulatory approach without compromising other important considerations, such as in this case patient safety and protection of intellectual property.

Former Commissioner of Food and Drugs and current CMS Administrator Dr. Mark McClellan, who took time from his busy schedule last week to visit Utah and meet with Senator Bennett and me and other Utahns on the new Medicare drug program, has recognized the confluence of medical, economic and regulatory forces at play.

Our society can ill afford to avoid a debate over the proper regulation of follow-on biologics. We simply cannot sustain over time programs such as Medicare unless we seriously explore what steps might prudently be taken to end an FDA regulatory system that effectively acts as a secondary patent for off-patent biological products.

Patient safety and product efficacy must remain at the forefront of this discussion. The task before policymakers is to consider how to maintain product safety and efficacy as we consider ways to eliminate unnecessary regulatory hoops for off-patent biological product license applications.

I will stipulate that it will be difficult to manufacture some generic equivalents of off-patent biologics. Some products will, no doubt, be more difficult than others to reverse-engineer. There will be technical issues galore. Some may actually prove impossible to

duplicate without trade secret information, but from what I have heard, many products will be able to be safely duplicated.

I believe that many, if not all, follow-on biologicals will require at least some form of human clinical testing. I also believe that the Federal Government would be very wise to consider providing taxpayer funding for the development of process validation guidelines that will help establish the critical manufacturing steps and assay parameters for medically or commercially significant off-patent biological products.

I also think it would be wise to consider commissioning or otherwise sanctioning studies by organizations such as the United States Pharmacopeia or the Institute of Medicine, in collaboration with the FDA and other interested parties, to identify and address the technical issues that need to be resolved in order to fast-track approvals for off-patent biopharmaceuticals.

I have known and worked with Acting Commissioner of Food and Drugs Crawford for many years. I appreciate him and the service that he has given to our country.

I look forward to working with you, Dr. Crawford, and other experts at the FDA on this important issue.

I know that Dr. Crawford will make this an important priority, and look forward to seeing the draft guidelines when they are issued later this year. I trust that Chief Counsel Dan Troy and Deputy Commissioner Amit Sachdev and Liz Dickinson and Jerilyn Dupont will provide sound legal and policy advice. I have great faith in all of them.

As a coauthor of the Drug Price Competition and Patent Term Restoration Act of 1984, I firmly believe that whatever we do on the legislative front should observe a principle of attempting to balance incentives for both pioneer and generic drug firms. While I am all for rolling up our sleeves to work to help develop an abbreviated approval system for off-patent biologics, we must be properly respectful of the intellectual property of the research-based firms because this is what undergirds the whole pharmaceutical enterprise.

As we proceed into this new era of drug discovery, it is important to ask whether our current intellectual property laws relating to pharmaceutical research and development are adequate to promote large-molecule, small-patient-population medicine in the future. For example, I have long thought the way we treat process patents under Hatch-Waxman should be reexamined in this new era of patient population medicine in which process patents will become more important and in which the relative importance of such patents will increase.

Difficult policy questions will crop up in a very difficult climate for the research-based pharmaceutical industry—of course, everybody's favorite whipping boy in an election year. Senator Lieberman and I have advanced an aggressive set of private sector incentives in our bipartisan bioterrorism bill. I plan to hold a hearing on the Lieberman-Hatch bioterrorism bill, and we urge that all interested parties review the IP provisions of this legislation and help us to get it right in every way.

Twenty years ago, we faced many challenges in fairly balancing the incentives and various interests when we came together on Hatch-Waxman. Frankly, I recognize that many in the bio-

technology industry believe that the creation of a fast-track approval process for off-patient biologics is the worst nightmare of a highly competitive, inherently risky industry struggling to attract the capital necessary to bring new products through FDA approval and into the marketplace.

Let me close by suggesting an alternative and perhaps preferable strategy to scorched earth litigation. Rather than just saying no, please consider engaging in a constructive public policy dialogue that focuses on identifying the legitimate scientific and legal obstacles that must be overcome in order to create a fast-track approval system for off-patient biologics. At the same time, come forward with ideas that will improve the legal environment for pioneer biotechnology firms. That is what we did back in 1984 and that is what we can do today if we all work together on follow-on biologics and other matters. If we have the right balance in the law, the American public only stands to benefit.

So this is a very important hearing. The information that we will receive here today will go a long way, I hope, to helping us to resolve these problems. But this is one of medicine's most important areas of study and it is one of the most significant areas of problematic work that we have ahead of us. And I just hope that we can all work together to do this in the best possible way and that we can keep this out of the realm of politics and put it in the realm of doing what is right. If we do that, this country will continue to be the major leader in the world and we will do a great deal for people all over the world.

With that, I apologize for taking so long, but I had to get these ideas out, and hopefully they will get out so that people can help us to do a better job here. We will turn to our Democrat leader on the Committee, Senator Leahy.

**STATEMENT OF HON. PATRICK J. LEAHY, A U.S. SENATOR
FROM THE STATE OF VERMONT**

Senator LEAHY. Well, thank you very much, Mr. Chairman, and I don't think any apologies are necessary. I think it is an extremely important issue and I applaud you for holding this hearing.

Dr. Crawford, it is good to see you. I should note that Commissioner Crawford and I worked together on a whole number of agricultural food safety issues when I was Chairman of the Agriculture Committee and you were at USDA. It is good to see you again. It was always good to see you back then.

I should note, Mr. Chairman, that Dr. Crawford and I were adding up the number—he has got one more grandchild than I do, but both of us put together don't begin to match you. So we will give you the crown on that one.

Biologic therapies fight life-threatening diseases and disorders, and I think we should all understand that. In many cases, these therapies are orders of magnitude more effective than drug therapies. The most famous biologic treatment saved millions of lives and has eradicated epidemics which, in the 1930's and 1940's, created mass panics each summer. Indeed, the first major outbreak of polio in the United States was in Vermont during the summer of 1894. You go around to some of our graveyards and you see the reference to that.

Rather than using the powerful tools of molecular biology, physicians back then willy-nilly came up with therapies such as concocting an emulsion from the ground-up spinal cords of polio-infected monkeys. They added other chemicals to that witch's brew, but one researcher, Dr. Jonas Salk, added formalin to the mix and, of course, the rest is history. This changes the lives of people for the better all over the world. I am old enough to remember the summer when all the municipal swimming pools would close and all the rest, the little iron lung things to put your money in for research.

Well, today, research for new biologic therapies is no longer an endless guessing game. Potent new technologies hold the promise to develop completely new classes of therapies to prevent, treat or cure otherwise inevitable or untreatable or incurable diseases. These new technologies are being focused on the horrors of cancer, cystic fibrosis, hemophilia, AIDS, Alzheimer's and multiple sclerosis. Those are just some of the many areas. For example, breakthrough biologic therapies such as Avastin starve cancer tumors of the blood supply that they need to grow. Activase greatly reduces the otherwise permanent disabling effects of strokes in adults.

Biologic technologies also hold out the best hope for those suffering from certain rare diseases that afflict 25 million Americans, including 58,000 Vermonters in my little State. But biologic therapeutics often cost far more than traditional drugs. One reason is they are a lot more complex chemically and they are more difficult to manufacture. I think we have to address this approval issue now because the patents on many biologic therapies are going to expire in the next few years.

With respect to drugs, Chairman Hatch and Congressman Waxman played crucial roles—I can't overstate what they did—crucial roles in developing a fast-track process to get less expensive, safe and effective generic drug alternatives into the marketplace under the Hatch-Waxman law. But a clear fast-track pathway doesn't exist for biologic therapies under our current law, so the critical question we face today is should Congress design a fast-track process for generic versions of these biologic innovations.

My own answer is yes, but only if what we do is based on sound science, if these alternative therapies are safe and effective, if they will help prevent shortages, and if these biologics would provide less expensive but potent alternatives for consumers.

I know that generic biologics are now available in Eastern Europe and Asia. Many point out that these biologics have been safe and effective and are less expensive than the original products in those countries. Others urge that we cannot be sure of the safety or legality of these products.

It may be that a sliding-scale approach is needed for the U.S. Perhaps the level of scrutiny should intensify with the increasing complexity of the molecules involved, the sensitivity of the formulation process, and the risks of deviation from the patent process. Science has to rule this decision, not politics, not greed, not the cloud of powerful vested interests. We need to do the right thing for millions of affected families. They are depending upon us to do the right thing.

I do want to work together to find a faster way to get more of these valuable therapies available at lower prices to consumers without sacrificing safety. The people who have these diseases, whether it is Alzheimer's, multiple sclerosis, or some of the other things I have mentioned—nobody asks whether they are Republicans or Democrats or independents. They are Americans. Throughout the rest of the world, there are so many millions more who are affected. We in this wonderful, great country can help find the cures, and we can do so much for the people of our own Nation and throughout the world, as we did with the polio vaccine.

So I hope all the stakeholders will participate in this process. The testimonies of Dr. Ben-Maimon and David Beier present a useful point and counter-point on both sides of this issue. Mr. Beier also raises complex trade secret issues. The bottom line, of course, is you have to have a careful balancing of interests and recognition of patent and trade secret rights.

We need to work together for the families who are going to be helped by this approach. I am glad we are beginning this. Again, I applaud the Chairman for starting these hearings. He knows and I know it could be a long road, but it is one where we all have to work together, for the benefits to the people of this great country are so huge if we do it right.

So thank you, Mr. Chairman, for doing this.

Chairman HATCH. Well, thank you, Senator Leahy.

Let me welcome our distinguished witnesses here today. On the first panel, we will have the Acting Commissioner of the Food and Drug Administration, Dr. Lester Crawford.

We welcome you to the Committee once again, Dr. Crawford.

Dr. Crawford has a distinguished career and we value his leadership in protecting the public safety. Most recently, he worked very hard to protect the U.S. food supply from the threat of mad cow disease and we are all grateful for his efforts.

In addition, I went to the opening ceremony for the new, unified FDA life sciences laboratory that is being built at the White Oak campus to replace the 38 different buildings throughout the region that are currently used for FDA offices. It is really a very, very impressive facility and I encourage all my colleagues to visit. Of course, it is just the beginning of that White Oak campus, but once we get that built—and that is pursuant to the FDA revitalization bill we passed over 10 years ago—once we get that built, there is no place in the world that will be able to compare from a food and drug regulatory standpoint with FDA, and that is long overdue.

I also want to extend a warm welcome to Dan Troy, who is accompanying Dr. Crawford this morning. Mr. Troy is the Chief Counsel of the Food and Drug Administration. These are two great public servants and I just want everybody to know it.

So we will turn the time to you, Dr. Crawford. We really appreciate the service you give.

**STATEMENT OF LESTER CRAWFORD, ACTING COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MARY-
LAND; ACCOMPANIED BY DANIEL TROY, CHIEF COUNSEL,
FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MARYLAND**

Dr. CRAWFORD. Mr. Chairman and members of the Committee, I appreciate very much the opportunity to be here and to participate in this important hearing on the subject of follow-on proteins.

FDA and the Congress share a great concern for senior citizens and other patients who have difficulty paying for prescription drugs. FDA has taken a number of significant steps to promote greater access to affordable prescription medications, including unprecedented steps to lower drug costs by helping to speed the development and approval of low-cost generic drugs.

Since its enactment in 1984, Hatch-Waxman has governed the generic drug approval process. In general, the law has been working well. Since 1984, over 10,000 generic drugs have entered the market and generics now account for close to 50 percent of prescriptions filled. The agency is now approving generic drugs at an average rate of one per day.

Medical innovation is a complex process, but one that can bring great value to patients. To realize the full benefits of medical innovation, it is important to adopt policies that protect incentives to develop new drugs and medical devices. Achieving this goal requires a delicate effort to strike a proper balance. Promoting innovation requires the right mix of incentives, safeguards and effective regulation to secure maximum benefit from safe and effective new medical technologies, while assuming mechanisms for broad and equitable access to these new treatments.

FDA has different statutory approval mechanisms for drugs and most biological products. I say most biological products because many biological products are also drugs, as that term is broadly defined in the Food, Drug and Cosmetic Act.

Traditionally, some natural-source proteins have been regulated as drugs, including insulin and human growth hormones, while other natural-source proteins such as blood factors are regulated as biological products. Currently, some proteins are licensed under the Public Health Service Act and some are approved under the FD&C Act.

FDA approves new drugs, as distinguished from biological products, under approval mechanisms found in Section 505 of the FD&C Act, and licenses most biological products under Section 351 of the PHS Act. Full, new drug applications under Section 505 of the FD&C Act and biologics license applications under the PHS Act require submission of complete reports of clinical and animal data to support approval.

For drugs approved under the FD&C Act, manufacturers can apply to FDA under Section 505(j) of the FD&C Act for approval of generic versions of the brand products after the patent and other exclusivity periods expire. This process is known as the Abbreviated New Drug Application, or ANDA, process.

Section 505(b)(2) also provides for the approval of NDAs supported by the scientific literature or by FDA's earlier finding that a drug is safe and effective. Both the ANDA and the 505(b)(2) approval processes incorporate consideration of the innovator's intel-

lectual property rights into the drug approval process. The ANDA process in Section 505(j) was established through the 1984 Hatch-Waxman amendments. This is an abbreviated approval mechanism for generic versions of drugs approved under Section 505 of the FD&C Act.

The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. By establishing that the drug product described in the ANDA is the same as the innovator drug product approved in the NDA, the ANDA applicant can rely on the agency's finding of safety and effectiveness for the drug.

The FD&C Act provides the ANDA and 505(b)(2) abbreviated approval pathways for drugs approved under Section 505 of that Act. However, the PHS Act has no similar provisions. The approval of generic or follow-on protein and peptide products has both scientific and legal dimensions.

First, as a scientific matter, FDA believes that for some protein products regulated under 505 of the Act, science has progressed sufficiently that we are able to assess the degree of similarity or identity between the innovator and a follow-on product. Prior to publishing a draft guidance document, FDA intends to have a major scientific workshop, in conjunction with the Drug Information Association, to explore this issue. FDA is still considering a separate process to address the legal and regulatory issues.

Today's hearing is an important part of that discussion and I thank you, Chairman Hatch, for holding it.

Chairman HATCH. Thank you, Dr. Crawford. In your testimony, you talk about many unanswered scientific, legal and policy questions about the follow-on versions of biological products approved under Section 351 of the Public Health Service Act that must be explored, and that the FDA plans on promoting public dialogue on these questions.

Now, what do you anticipate some of these questions to be, and how will FDA promote public dialogue to find answers to these questions?

Dr. CRAWFORD. Well, what we will do is, as I announced, we are going to have this scientific workshop. We will be joined by the Drug Information Association and it will be a well-managed workshop where questions will be posed to the participants, and it will be structured in such a way that we come out with a set of common understanding about what is needed in order to regulate follow-on proteins, as they are generally called. We also will get information from deliberations that the European Union has had on this same subject, and also from other trading partners around the world.

But what we really need is to determine how do we go through the scientific and regulatory process of ascertaining that a product is either identical or has enough characteristics in terms of the active ingredient of the molecule to where we can declare it is, in fact, worthy of consideration as a generic.

The term "generic," as you know, essentially means "the same," and we are not sure, with the kind of science that we have, that, in fact, we are ready for that kind of determination with many of these large molecules, as you put it in your opening statement. So

we need help in this direction. FDA has not made its mind up about it. We need to know more about the science.

We find, as you know, that we get great answers from industry because they are dealing with the problems everyday, and we look forward to involving them in this process, as well as the academic, medical and scientific communities.

Chairman HATCH. As you know, the cost of prescription drugs has been an issue of importance to many Americans, and Congress has been working on various legislative proposals to try and address this matter. I believe that enacting the Medicare prescription drug law last year was a step in the right direction. All Medicare beneficiaries will soon have access to the Medicare prescription drug program, and lower-income beneficiaries will receive significant help and relief from their drug expenditures.

The Medicare prescription drug law encourages drug plans to offer generic drugs to Medicare beneficiaries when appropriate, which is one important way to find savings. Now, in fact, in your testimony you state that generic drugs typically cost 50 to 70 percent less than their brand-name counterparts, and that they are bioequivalent.

Now, according to CBO, generic drugs save consumers an estimated \$8 to \$10 billion a year at retail pharmacies. I was told by Mark McClellan just a few days ago that actually that figure is even higher today as a result of Hatch-Waxman that consumers are saved.

Do you believe that generic biologics, if they could be developed, would provide Americans with similar savings?

Dr. CRAWFORD. I think it is too soon to say. As I mentioned, the European Union is moving in sort of the same kind of direction, but no country or group of countries has experience with this to the extent that they can say what the savings would be.

These are difficult molecules, as all of you know, to characterize, and so how many generics, if you will, once we work out the regulatory and scientific issues, will enter the market for each one that is approved as an innovator product we can't say at this time. We do know that some biologics are, as you mentioned, very costly indeed. And so even the introduction of one other competing product will surely lower the cost, but it is not possible to say whether or not it will be the same percentage as the 50- to 70-percent figure that we have with standard drugs.

Chairman HATCH. Okay. Now, to what extent do you think Section 505(b)(2) of the Food, Drug and Cosmetic Act applies to biologics? You might want to have Mr. Troy help us with that one as well.

Dr. CRAWFORD. I would very much want to have Mr. Troy join me. He is our chief counsel.

Chairman HATCH. Well, I think it would be good to have his testimony on that.

Mr. TROY. Thank you, Senator Hatch. 505(b)(2) by its terms applies only to the Food, Drug and Cosmetic Act and to 505 products. FDA does not believe that 505(b)(2) applies by its terms to products that have been approved under Section 351.

But as Dr. Crawford mentioned, there are a variety of proteins, human source proteins—insulin, human growth hormone and oth-

ers—which have been approved under the 505 pathway, in part some of these for historical reasons. So where the science and the law is there, we believe that follow-on proteins may perhaps be provable using 505(b)(2).

Chairman HATCH. Well, that is helpful. Just keep helping us up here to understand this, okay, because this is complex to all of us.

Senator Leahy, if you would care to—

Mr. TROY. Sorry. I talk too much like a lawyer sometimes.

Chairman HATCH. Well, I am glad to hear that, to be honest with you.

Senator LEAHY. You would be surprised the number of lawyers who show up here at all kinds of hearings, and some even on this side of the dais.

Chairman HATCH. And I can say some are better than others, too.

[Laughter.]

Senator LEAHY. That is true. Of course, those on this side, both Republicans and Democrats, are the best, but that is okay, although I must admit there are days when we are here that I miss those days in the courtroom.

Commissioner Crawford, as I said earlier, it is good to see you again.

Dr. CRAWFORD. Thank you, sir.

Senator LEAHY. I have always enjoyed working with you.

In your written testimony, you raise concerns about being able to assess the relative sameness of generic alternatives derived from biological sources because of the complexity of protein structures. But then you state, “However, the science of characterization has progressed to the point where it is becoming possible to make such assessments for some products, and we expect that science will continue to progress.” Some of the European and Asian countries would say they are ahead of the U.S. regarding developing an accelerated process to approve these generic biologics.

Are you considering recommending to OMB any legislative proposals for Congress to review to take advantage of the technological advances, those that might allow scientists to make accurate sameness evaluations?

Dr. CRAWFORD. We are not at this time proposing legislation. As I mentioned, we are going to have this scientific workshop in conjunction with the Drug Information Association. At the conclusion of that, we will weigh what we have found out and determine which fork in the road to take. But at this point, we are not prepared to say whether or not we would—

Senator LEAHY. Well, after that, could you let Chairman Hatch and myself know where you are going with it? It would be nice to have us all in the same hymn book, the Congress and the administration.

Dr. CRAWFORD. Absolutely.

Senator LEAHY. At some point, there is going to be required some legislation. For example, David Beier’s testimony raises some concerns about protecting the confidentiality of proprietary business data and trade secret information. He points out that the FDA recently noted that data required for the approval of any new product must be in the public domain.

How do you handle trade secrets and proprietary information? I mean, you have to do your job, but the companies have to be assured, if they are spending millions of dollars on something, that their confidential information is kept confidential. How do you do that balance?

Dr. CRAWFORD. I am going to ask Dan to comment on that, but before he does, ever since I was first in the FDA, in 1975, as you know, we have had great difficulties as the science changes, and so forth, in maintaining the confidentiality. But FDA has always had as a top priority the maintenance of trade secret information, and I think our record is quite good on that.

Dan?

Mr. TROY. I want to pick up on what Dr. Crawford said. Congress has decreed that trade secret and confidential commercial information is not disclosable by us. Indeed, it is a crime to disclose trade secret information under an act of Congress.

I think as a result of that, one of the most salutary aspects of FDA's culture is the care that people at FDA take with the very valuable business information that is entrusted to us. I think people really have an appreciation about how valuable it is. I am not saying there are never any missteps, but by and large there is a really good culture there of protecting that confidential commercial and trade secret information.

The upside of that, of course, is that companies develop that information and can submit it to us with a fair degree of confidence that we are going to preserve it. Of course, as comes up in, for example, the whole debate about clinical trials, at times there are profound interests on the part of people in the patient community, in the medical community and in the scientific community who want access to that information.

There is no doubt that that is a tension that we have to navigate, and I think that it is a tension that comes up in this context as well. On the one hand, if we don't preserve this intellectual property, then people aren't going to do the work to develop the new products. On the other hand, if we give perpetual protection to the intellectual property, then you will never have follow-on proteins or generic biologics.

The brilliance of Hatch-Waxman is that it struck a balance between innovation and intellectual property protection and, at an appropriate time, a pathway for allowing products to come to market that are less expensive and more affordable and more available. So it is precisely that balance between innovation, which in this industry primarily manifests itself as intellectual property protection, and affordability that we are going to strive for, and we are going to work with Congress to strive for because I think there is pretty broad agreement that we are not going to be able to do this alone.

Senator LEAHY [PRESIDING.] Thank you. Senator Hatch had to leave for a vote—he is coming right back—in another committee. I have to leave for a similar thing. You are both aware of how they usually try to have us on 12 different things at once, especially as we come close to a time as we are when there is going to be a break.

So I am going to turn it over to Senator Durbin. It is all yours. Wreak all the havoc you want.

[Laughter.]

Senator DURBIN. Be careful what you wish for.

Let me thank the witnesses for being here, and especially thank the FDA as an agency. In the time I have served on Capitol Hill, I have had a good working relationship on the Appropriations Committee with the FDA.

Dr. Crawford, I thank you.

Dr. CRAWFORD. Thank you, sir.

Senator DURBIN. Mr. Troy, we don't have a long friendship or relationship, but I am glad that you are here today and I thank you for your testimony.

Let me try to explore an element here that I think needs to be discussed, and that is the market dynamic—and I think, Mr. Troy, you alluded to it—to protect the intellectual property of the company that discovers the chemical drug or the biologic drug, but only to a certain point at which we decide that their vested interest in that property becomes a public interest.

We moved to Hatch-Waxman in 1984 with the belief that generic drugs are of public value because they save consumers money. You referred to the brilliance of Senator Hatch and I think he caught that as he was leaving the room, and I hope he did, and I want to give credit to both him and Congressman Waxman.

But it is also true from your testimony, Dr. Crawford, that this was not an altogether smooth transition. There was some resistance from some pharmaceutical companies under Hatch-Waxman which led to the 2003 directive from the FDA concerning how long you could test the movement from brand name to generic, and that had become abusive; the conduct of the industry had become abusive.

So address for me, if you will, for a moment the market dynamic when it comes to this issue. Are we not dealing with the same thing that the original company that has developed the protein or the biologic has a market interest in maintaining exclusivity in terms of production as long as possible because it is a profitable thing, and that we understand that at some point it may move to a generic or follow-on at lower cost?

You have addressed, or at least alluded to the scientific challenge of producing the follow-on in a product that is different from some chemical drugs. But speak to, as well, about the market aspect of this. What kind of resistance is the FDA running into from those who have patent on the original biologic and the profitability of that medicine who believe that moving to the follow-on is going to end their profitability. Is there a resistance there that is part of this equation?

Dr. CRAWFORD. Well, there is a great deal of interest in what we are doing here, it is fair to say. But what we have heard from the industry and the relevant trade associations is that I think there is a willingness to help FDA define through appropriate intercourse what it is that we need to do in order to ascertain that there is sufficient sameness between the pioneer product and the generic product to allow the process to move in a fair and equitable manner.

We are going to need cooperation from industry, but also from manufacturing experts, the academic community, chemical and

medical community, and so forth. So we have got to start this dialogue and I don't really know where it is going to end up, but we are going to open up with this scientific workshop and then that is going to lead us into other directions.

At the same time, we are going to have a separate consideration of the legal and regulatory aspects, but I think we have got to get the science first. So to answer your question, I wouldn't call it resistance, but there is a great deal of interest in what we are doing and I think the public, in general, wants to be part of the process and I think that is a good sign.

Senator DURBIN. How important is the cooperation of the brand name biologic manufacturer in developing the science and developing the process that leads to the follow-on biologic?

Dr. CRAWFORD. Well, I am going to ask Dan, if I may, to respond to that. But, obviously, the attitude of the industry both in the pioneer companies and also those that are seeking to get a generic status—there is a tension there, and there also is an interchange which sometimes is dictated by the courts, as you know, that is very important to the process.

Dan has had a great deal of experience over the last 3 years dealing both in courtroom situations and also in the adjudication of some of these disputes. He is an expert in this area of the law, so I would like to ask him to comment.

Mr. TROY. Thank you. I think it is actually a bit of a mistake to suggest that the innovator industry, at least from what I have read and what I have heard, is united on this issue. I think there are different camps that people fall into. Different companies are looking at different positions, and so I don't think what we are seeing is some uniform innovator brand company resistance fighting this issue tooth and nail. I think there is a recognition that sooner or later the time is going to come. A lot of it will depend, of course, on the science.

When you say we need the cooperation ultimately—of course, you can pass legislation with or without somebody's cooperation. Normally, you get someone's cooperation to one extent or another. Ultimately, we do administer Hatch-Waxman, one might say, with the cooperation of the brand industry. They give us the data to approve their product. Then we can, and do, under Hatch-Waxman rely on that data in approving an ANDA.

They don't play any role in that process at that point. On occasion, they might raise scientific or legal objections to what we are doing. We are pretty good, I think, at separating out the wheat from the chaff and recognizing when challenges are being raised that are frivolous or challenges that are raised that are real and substantial that we need to deal with.

So I think that, as Dr. Crawford reflected, we are still at a very nascent stage. We are exploring. I think people are figuring out where they are. There is still a lot of public process to undergo, and a lot of scientific and legal and regulatory exploration.

Senator DURBIN. If I could ask one last question, Mr. Chairman, this is a question which relates to your agency, Dr. Crawford, and it relates to this issue, certainly, but many others.

Having watched your agency over 20 years and watched its budget, I continue to marvel at how much you get done for the amount

of money that we send out to you, and how much we rely on you to get it done. The approvals, as you know better than most, involve virtually every aspect of human life. The FDA is in there and involved in it.

So when we talk about this kind of undertaking which is clearly going to require some of the best and brightest, and talk about whether or not we can develop a scientific process and say with some certainty that there is a follow-on biologic that can be trusted and is at a lower cost, where do you stand in terms of resources, particularly in personnel and lab space and whatever is necessary, to meet this challenge and so many others that we throw your way?

Senator Hatch and I were on the floor yesterday talking about another issue which we won't go into here, but one of the elements of it was, well, the FDA needs more manpower, more people to get this job done. So in light of everything that Congress keeps heaping on your agency, FDA, including this, where are you?

Dr. CRAWFORD. Thank you for that question.

[Laughter.]

Dr. CRAWFORD. It is certainly one that I can expand on as much as you like.

Senator Hatch mentioned the White Oak campus, and the idea there is to get the expertise of FDA, at least on the medical products side, the three centers there, plus the support staff above, including me, located in the same place so that we can have a critical mass of scientists like oncologists, and in this case pharmacologists, people that work in biologics of all sorts.

If you can get them working on the same campus instead of—actually, we have about 38 different facilities. If you count the mail facilities, we have 55 in the Washington area, and it increases every year a great deal. That is the single greatest impediment to getting our job done.

We have Committee meetings of very key people to review applications that involve 70-mile round trips for our scientists. They generally have to travel on Washington's Beltway system, so you can imagine managing FDA, such I am charged to do, and what a great difficulty that is.

Apart from that, there is good news. We are now up to the largest number of personnel that we have ever had in FDA, and the recent increase is due in large part to the Congress dealing with the bioterrorism problem and providing both funding and personnel to deal with that. So the big increase has been there and not in the medical product area. In other words, it has been in the field forces.

But it has helped a great deal because in the late 1970's we lost 10 percent of our personnel and it has taken all this time to get them back up to that level, and we are now even past it. The other good news is that Congress has allowed incentive pay and locality pay, so that we are able to pay physicians, for example, and other health care professionals competitive salaries. They are low-end competitive, to be sure. I wouldn't say that things are perfect there, but when we are about to lose someone to another company or even to another government or something like that, we are able, by ag-

gressively extending the authorities vested in my office, to save a lot of these people.

The turnover at FDA down through the years that I have been associated with it is—a healthy rate is estimated to be about 8 percent. You need some turnover, as you well know, but what I need to be very careful of is whether that turnover is happening in key pockets. I mean, if the agency level is 8 percent and then in key scientific areas you are losing 25 to 50 percent a year, then you still have got just a big a problem. So far, so good in that respect. In the two-and-a-half years I have been back at FDA basically being the chief management officer, we have stabilized that very, very well indeed.

We do have a precarious level of budgeting. It is about \$1.8 billion, and as you would know, we have got to make really good use of that. We have less and less discretionary funds and we can't leave anything that we are charged with regulating high and dry. We have to retrain people, and also multiply-train them.

One of the things that has helped under the Bioterrorism Act is that we are able to commission other agencies to do FDA's work in key spots. In order to cover the border with products coming in, not just food, but drugs and other things, we have taken major advantage of that provision, which was a great boon to FDA, and we have now commissioned 7,500 Customs and Border Protection agents to do FDA-type work. We do that after training and we do that after staying in contact with them.

Also, each year in the budget we try to plan for things like BSE, the cattle disease. And I would give my predecessors a lot of credit for asking for the funding that we needed in order to stay up to date on that and to prepare for the inevitability.

I will stop there, but if you want more, you can get it.

Senator DURBIN. Well, thank you. Mr. Chairman, I think we all understand that as important as these discussions are, the implementation of our good ideas depends on the professional men and women at the FDA who can get the job done.

While you were out, we lavished praise upon you for your work with Congressman Waxman, and your staff will verify that what I say is true.

Chairman HATCH. Well, that is unusual on this Committee.

[Laughter.]

Chairman HATCH. While I have you here, I want to take advantage of this for a minute because there are a couple of other questions that I have that I hope will amplify.

I know you are going to be holding a public symposium on follow-on biologics. I would like more details on the guidance your agency will be issuing on follow-on biologics. First, and most important, when will this be issued? Secondly, what will be addressed in the guidance that you will issue? This is an important matter, I think, not just to me, but to many people, and I would be interested in your thoughts on that.

Dr. CRAWFORD. Well, Senator Leahy while you were out also brought this subject up of wanting to know what we find in the scientific workshop. I think what would be appropriate, with your concurrence, would be, following the workshop, we should come down and brief you and your staff and the other members of the

Committee, as appropriate and as they are interested, on what we do find and where we think it is going to lead us.

Chairman HATCH. Do you know about when that would be?

Dr. CRAWFORD. Well, we hope to have the workshop by the end of the summer.

Mr. TROY. I think in the fall, early fall.

Dr. CRAWFORD. Your concept of fall and mine are different, as a matter of fact, because you are an attorney.

[Laughter.]

Chairman HATCH. It is a disability, I have to admit.

Dr. CRAWFORD. I am pressing, Senator, to have it done maybe the day after Labor Day or something that, and we will come and see you when that does happen. When we turn that into guidance will actually depend on what we find out through this fact-finding process.

Again, we are pressing very hard to get something out, but I have to plead that we don't know what we will find out in the scientific workshop and so I can't project. We may find out—you know, we are open-minded about this—that the science is still lagging in terms of characterization of these products, and so we need to fund some research projects or something like that. So I have to answer it that way.

Chairman HATCH. Well, we will be interested in what kind of policy you come out with in that.

Dr. CRAWFORD. Thank you.

Chairman HATCH. Let us know as soon as you can.

Could you give us more details on major policy decisions that we would face in devising a system to regulate follow-on biologics? And then Senator Leahy mentioned trade secrets. Could you or Mr. Troy amplify on that and the other major issues that we will all be facing?

Dr. CRAWFORD. Yes. I would like to ask Dan to handle that part.

Chairman HATCH. Okay.

Mr. TROY. I guess I am not quite sure I understand what the question is, to address what the trade secret issues are?

Chairman HATCH. Yes.

Mr. TROY. We talked about that a little bit while you were gone. Congress has prohibited us from revealing trade secrets, and we are very protective of trade secrets and confidential commercial information.

That said, at a certain point information becomes sort of generally known, and generally known in the scientific community. Part of the challenge is figuring out at what point does information kind of cross over. Obviously, if there is literature about something, then that is easy.

But I think it is fair to say that the agency has always been extremely protective of intellectual property. That is one of our key missions. It is a key part of our culture and the challenge in going forward, which you are well aware of because that is what you did in Hatch-Waxman, is to strike a balance between the intellectual property protections and making products accessible and affordable.

Chairman HATCH. Well, one other thing. This Committee will be holding a reimportation hearing in the near future. I would like

you to be ready to come to that. We are going to need your testimony on that.

Dr. CRAWFORD. Well, we look forward to that. As you know, this has been something FDA has been heavily involved in for some time and we look forward to some reasonable solution to it. As you also know, our concern by statute and also by the thing that drives us to be public servants is the safety and effectiveness of these products. So we have concerns about that. We would be very pleased to share that with the Congress, this Committee and anyone else who is working in that particular area.

Chairman HATCH. Well, thanks, Dr. Crawford. For the record, one of the questions that we may submit in writing—and I will keep the record open until the end of the day for any questions any member of the Committee has in writing—we would like you to not only comment on trade secrets, but also any other major factors that will be discussion points on how to regulate follow-on proteins, if you could do that for us.

Dr. CRAWFORD. We will be happy to respond to the question in writing if we could.

Chairman HATCH. If you could, I would appreciate it.

Dr. CRAWFORD. Thank you.

Chairman HATCH. We appreciate both of you being here. We think you are both great public servants and you have been doing tremendous work out there. I can't wait until you not only have that central campus so that the administrators don't have to travel all over 38 different places all over this area, but you will have the highest and the best scientific instrumentation and facilities to work with, which is something that we owe to you and that you need to have done. So I hope you will keep the pressure on Congress to finish the White Oak campus.

Dr. CRAWFORD. Thank you for all your support, sir.

Chairman HATCH. Thank you. It is good to have both of you here.

[The prepared statement of Dr. Crawford appears as a submission for the record.]

Chairman HATCH. At this time, I would like to introduce our second panel. First, we will have Mr. Bill Schultz, who is testifying on behalf of the Generic Pharmaceutical Association. Mr. Schultz is a partner with Zuckerman Spaeder, who practices in food and drug law, complex civil litigation, products liability and appellate litigation. Mr. Schultz also was the Food and Drug Administration's Deputy Commissioner for Policy and was responsible for overseeing the development of all FDA policies and regulations and FDA legislation.

Most of us remember Bill when he was the FDA counsel to the former Chairman of the Health and Environment Subcommittee of the House Energy and Commerce Committee. While working for Congressman Waxman, he did assist greatly in the development of food and drug and other health care legislation.

I have great respect for you, Bill, and we are glad to have you here and welcome you here.

Second, we will have David Beier.

David, we are glad to see you again and glad to have you helping us on this Committee.

David is the Senior Vice President of Global Governmental Affairs for Amgen. Mr. Beier was former Vice President Gore's chief domestic policy adviser, and prior to that position he was Vice President of Government Affairs and chief lobbyist for the biotech company Genentech, where he developed expertise in intellectual property, taxation, health care and other issues. Mr. Beier also worked for the House Judiciary Committee under former Congressman Pete Kastenmeier, of Wisconsin.

We are delighted to have you here and I have appreciated your advice through the years.

Our next witness is Dr. Carol Ben-Maimon. She is the President and Chief Operating Officer of Barr Research. Dr. Ben-Maimon is responsible for all aspects of Barr's proprietary product research and development activities. She is also responsible for managing the company's expansion into biologics.

Prior to joining Barr in 2001, Dr. Ben-Maimon served as Senior Vice President for Science and Public Policy-North America for Teva Pharmaceuticals USA, where she coordinated Teva's U.S. and Canadian research and development efforts, product selection and global integration. Dr. Ben-Maimon joined Lemon, owned by Teva, in 1993 and served as Vice President of Medical and Regulatory Affairs from 1991 until 1993. Dr. Ben-Maimon was Director of Clinical Pharmacology with Wyeth-Ayerst Research.

So we are grateful to have you take the time to be with us as well.

Our final witness on this panel is Dr. Bill Hancock. Dr. Hancock is Bradstreet Chair in Bioanalytical Chemistry, Barnett Institute and Department of Chemistry and Chemical Biology, of Northeastern University in Boston, Massachusetts. Prior to joining Northeastern University, Dr. Hancock was the editor-in-chief for the Journal of Proteomic Research of the American Chemical Society. He was also Director of Analytical Chemistry at Genentech and a visiting scientist at the FDA in the mid-1980's.

Dr. Hancock has received numerous awards and honors, including the American Chemical Society Award in Separation Science, in 2003, and the Martin Gold Medal in Separation Science in the year 2000. Dr. Hancock has contributed to numerous industry publications and organizations.

The good news is this hearing is a unique opportunity to see a former Gore domestic policy adviser debate a former Nader disciple. The bad news is that our topic is so esoteric that only a handful of people listening will have any idea what they are talking about.

[Laughter.]

Chairman HATCH. Of course, that is not unusual for those two candidates anyway, you know.

[Laughter.]

Chairman HATCH. I am only kidding. Seriously, I look forward to hearing all of the witnesses' testimony today and we are very grateful that you have taken time to come and help us to understand these things better on the Committee. This is an area where we all need to work together in the best interests of our people and of people throughout the world because if we are successful in this

area, we may very well be able to transcend anything we have been able to do up until now.

So we will start with you, Mr. Schultz. We will go to Mr. Beier, then Dr. Ben-Maimon, and then finally wind up with Dr. Hancock.

STATEMENT OF WILLIAM B. SCHULTZ, ZUCKERMAN SPAEDER LLP, ON BEHALF OF THE GENERIC PHARMACEUTICAL ASSOCIATION, WASHINGTON, D.C.

Mr. SCHULTZ. Thank you very much, Chairman Hatch. I appreciate this opportunity to testify on behalf of the Generic Pharmaceutical Association, the trade association whose 120 members produce more than 90 percent of all generic drugs in the United States. We owe our existence to you and to the Hatch-Waxman Act which was passed 20 years ago and which has been such a tremendous success.

In 1984, we were at a crossroads. The brand industry was flourishing, and yet FDA had no regulatory pathway and no system which provided for generic versions of most of these brand products. So even after their patents expired, brand companies continued to sell their products at monopoly prices because they had monopolies. Congress responded and enacted the very successful Hatch-Waxman Act.

Today, we are at a similar crossroads, Mr. Chairman, only this time it is for what we call biopharmaceuticals, as opposed to the traditional pharmaceuticals. As you said in your opening statement, biotechnology products account for something like \$33 billion in pharmaceutical sales, and the sales are growing. Many of the large-selling biotech drugs have come off patent already or they will soon. More important, in contrast to the traditional drugs, these have exceedingly high costs, in the thousands of dollars per patient per year. So the potential savings and the stakes for the health care system are enormous.

It is also significant that other countries are actively implementing such a program, including countries in the EU, Asia and Latin America. In fact, the EU issued guidance 3 years ago to assist the industry in bringing generic biopharmaceuticals to the market. As the world leader in pharmaceutical development, the U.S. should take on a leadership role in the development of a viable framework for generic biopharmaceuticals.

I now would like to address several specific questions. First of all, does the FDA have the legal authority to approve generic biopharmaceuticals? We believe the answer is clearly "yes". As explained in my testimony, the FDA can adjust data requirements for generic biopharmaceuticals.

Second, if the FDA can act in this area, is there any need for Congress to do so? The answer here is "yes", as well. FDA, left to its own accord, could take years to resolve the questions of its legal authority and to promulgate regulations. And years of litigation will follow that, inevitably. Our health care system cannot afford to lose this precious time, especially given the fact that there are, as Senator Hatch said, already 150 biopharmaceutical products on the market, with more to come in future years. It is just like 1984, Mr. Chairman. Congress needs to step in. It is appropriate for it to do so.

Third, should Congress wait for all the scientific issues to be resolved before it acts? This seems to be some of the brand industry's argument. The answer here is "no". As former commissioner Mark McClellan recognized this year—and this is a quote—"We do believe that the science may be adequate now to proceed on several relatively simple biologics." In other words, Mr. Chairman, the science is already there for some biologicals.

In my written testimony, we have given examples of situations where FDA has already reduced data requirements for certain biotech products that match ones previously approved. It may be some time before we can do this for other products. Yet, Congress should give FDA the legal authority and the direction to solidify a generic biopharmaceutical approval program.

For each product, it will be FDA, not Congress, that will be charged with determining what the approval criteria will be and what will be necessary to support a generic product. Simply put, sound science must drive the system, but there is no reason to wait to legislate in this critical field.

There is one telling example which by itself rebuts the brand companies' argument that interchangeability between the generic and the brand is not possible. GlaxoSmithKline sells a Hepatitis B vaccine called Energix-B that is made through biotechnology. Merck sells a similar product called Recombivax HB. The FDA-approved labeling for both products states that these vaccines are interchangeable with each other, and that either may be used to create the vaccination course initiated with the other. Importantly, FDA has allowed this interchangeability to be established without anything like a full set of data.

The fourth question: Would it be unconstitutional for FDA to rely on the brand drug's approval? Would it be a taking of property without just compensation? Don't worry. I am not going to spend the time that is really needed to engage in a constitutional debate here, and the Association will be submitting shortly an analysis of this issue.

But I believe that it is clear from the Supreme Court jurisprudence in this area that the Court has gone nowhere as far as is often claimed by the industry. Government agencies rely on information submitted by companies and permit other companies to rely on agency action based on this information all the time.

FDA, for example, regulates food additives by regulation. After a company submits its data, FDA issues a regulation, and the next company can rely on that regulation to get its approval. Of course, it has to wait for patents to expire and other intellectual property protection, but it can rely on the approval. It is not taking the data; it is relying on the approval.

We have a similar system for over-the-counter drugs. We have a similar system for medical devices. The first company gets its approval. If the second company's product is substantially equivalent, it can get its approval as well. These systems have been in place for many, many years and no one has ever argued there is an unconstitutional taking.

Fifth, what should be the regulatory system that permits FDA to approve generic biopharmaceuticals? What should such a system look like? There are several important parameters. First, the sys-

tem needs to allow FDA the flexibility to tailor pre-clinical and clinical data requirements for biopharmaceutical products. The complexity of these products varies along a continuum. Some are very close in complexity to chemical drugs and some are much, much more complex.

FDA should have the authority to establish the appropriate requirements based on a scientific risk/benefit approach. Congress needs to, however, require FDA to impose only those regulatory requirements that are necessary to ensure safety and efficacy. We faced this issue in 1984. There was a lot of concern that FDA would over-regulate. Congress was very careful in the statute and was very successful in ensuring that didn't happen. This is something to keep in mind here, but we want full regulation to ensure safety and efficacy.

We urge Congress to direct FDA to be very active in advising generic companies about how to comply with study design, data requirements and other issues. And we urge Congress, once it enacts legislation—and I believe it is inevitable that Congress will enact this legislation—to periodically monitor FDA and perhaps require FDA to issue regular reports back to Congress.

In conclusion, Mr. Chairman, we ask for your help. As a result of the 1984 Hatch-Waxman Act, the generic drug industry now includes highly sophisticated and substantially capitalized companies that are ready to enter this market. A significant number of today's biopharmaceuticals are ready for generic versions. An effective and efficient generic biopharmaceuticals program will result in tremendous untapped cost savings to this Nation's health care system.

In other words, today the case for legislative action is as strong as it was in 1984. The problem demands your attention. We thank you for this hearing and the generic industry stands ready to assist you in any way that we can.

[The prepared statement of Mr. Schultz appears as a submission for the record.]

Chairman HATCH. Well, thank you so much. We appreciate that excellent testimony.

Mr. Beier, we will turn to you. We are glad to have you here.

**STATEMENT OF DAVID BEIER, SENIOR VICE PRESIDENT,
GLOBAL GOVERNMENT AFFAIRS, AMGEN, INC., WASHINGTON, D.C.**

Mr. BEIER. Good morning, Chairman Hatch. On behalf of Amgen, the world's largest biotechnology company, I come before you this morning with a simple message: Put patients first and sound policy will follow. We believe there may be a role for follow-on biologics in the marketplace if patient safety is assured and innovation is encouraged and protected.

Everyday, over 80 Americans discover that they have leukemia. In the past hour, 150 Americans learned that they have diabetes. For each of these patients, there is only one issue before them: hope for access to safe, new cures and treatments. The best and brightest hope for breakthroughs for these patients comes from the United States biotechnology industry.

Almost half of the new medicines approved by the FDA last year were biological products, and over 300 biotechnology products are

currently available in Phase III trials. As Kenneth Shine, the head of the Institute of Medicine, said, the 20th century was the century of physics and astronomy. The 21st century is going to be the century of biology and life sciences.

Let me be perfectly clear. Biological products are not the same as drugs. As the picture on the chart demonstrates, they are very different—very, very different in terms of their size and complexity. Biological products are immensely more complicated to manufacture, and therefore to reproduce by another manufacturer. That is why there needs to be a unique model for the approval of follow-on biologics.

My colleague, Bill Schultz, referred to 1984 and claimed that it was an analogous situation. In 1984, there were hundreds of profitable pharmaceutical companies, tens of thousands of drugs, and one-third of the leading 200 drugs were already subjected to generic competition. The FDA had previously issued a scientific regulation outlining the circumstances for the approval of a generic product.

In 2004, there are 1,100 biotech companies. Only a handful of them make money. There are only 155 products on the market and there is no regulatory pathway, no scientific basis for the approval of follow-on products until and unless a process like the one Commissioner Crawford outlined takes place.

As the FDA recognized this spring in its Critical Path Report which analyzed trends in drug innovation and development, there is a substantial risk that the promise of biological breakthroughs will not fully bear fruit in part because of increased complexity and expensive development. With these increased risks comes the need for strong incentives for innovation.

Mr. Chairman, as the author of Hatch-Waxman and as a supporter of innovation through other mechanisms such as orphan drug and pediatric exclusivity, you know firsthand the power of strong but fair patents, data exclusivity and trade secrets to spur investment, innovation, and ultimately for breakthroughs for patients. As the Supreme Court said in the *Benito* vote case, the intellectual property system is a carefully crafted bargain, much like the one you crafted in 1984, Mr. Chairman.

This morning, we start and end with patients. Patients benefit profoundly when there are balanced incentives to innovate. Patients are also benefitted when they know, after a complete public and science-based process, that medicines they take are completely safe and completely effective.

Current law does not provide the FDA with authority to approve follow-on biologics. We welcome the invitation from this Committee to begin a dialogue about a regulatory pathway for follow-on biologics. We believe that Congress must protect innovation before the FDA proceeds with the first steps toward a rulemaking or even a public process leading to guidance on science issues.

What do I mean by protection for innovation? In sum, it is the combination of patents, data exclusivity and trade secret protection. Billions of dollars of reasonable, investment-backed expectations rest on the maintenance of these rights. These rights benefit patients by promoting research and development for new breakthroughs. They protect the invention, usually in the form of a prod-

uct patent, or, often for biotech products, the process. They also protect the pre-clinical and clinical trial data created by an innovator at the cost of hundreds of millions of dollars. This data exclusivity is an integral component of innovation protection. Finally, the proprietary formulas, especially the detailed manufacturing specifications, are protected under Federal law as trade secrets.

As an innovator, Amgen does not seek to extend our legal rights beyond the metes and bounds of existing innovator protections. On the other hand, we would be concerned if the FDA seeks to rely on our proprietary data to approve a follow-on product.

To respond to Mr. Schultz' comments, it is true that the FDA in other analogous regulatory systems relies on the approval of other products. But as he carefully noted, they do not rely on the underlying data of the innovator. Our concern is about whether the agency would pierce our trade secrets and knowledge of our manufacturing process and use that information to approve a follow-on product.

Finally, let me briefly address a topic not directly before the Committee; that is, what are the appropriate regulatory rules that would permit the approval of a follow-on product.

In the main, we believe that pre-clinical data, clinical trials to demonstrate safety and efficacy and robust post-approval safety surveillance measures will be necessary. I stress these points because some of the other witnesses before you today indicate that they want to look to precedents in either China or Lithuania. Those systems do not have those elements and in some instances don't protect the intellectual property of the innovators.

While the exact standards for follow-on products will vary from product to product, there need to be some irreducible minimum data standards before an approval can be granted. Why do we take this view? First, we believe that significant or major manufacturing changes in biologic products made by anyone, including the innovators, need robust data submissions.

Second, because biologics, especially complex proteins like the one outlined on the chart, are unique mixtures of active species, it is literally impossible for a second manufacturer to copy or duplicate the original product. Significant changes in cell lines and the manufacturing process to produce these products thus require a profound level of investigation, which can include pre-clinical and clinical data, before any reasonable regulatory authority can assess the safety and efficacy of these products.

In closing, we welcome this invitation and express our continued interest in working with you, Mr. Chairman, and the Congress and the FDA to fashion reasonable rules for follow-on biologics, including the protection of innovator rights and measures to assure patient safety.

Thank you.

[The prepared statement of Mr. Beier appears as a submission for the record.]

Chairman HATCH. Well, thank you so much.

Dr. Ben-Maimon, we will take your testimony.

**STATEMENT OF CAROLE BEN-MAIMON, M.D., PRESIDENT AND
CHIEF OPERATING OFFICER, BARR RESEARCH, INC., BALA
CYNWYD, PENNSYLVANIA**

Dr. BEN-MAIMON. Thank you for inviting me here today. My experience as a physician and in both generic and propriety drug development provides me, I think, a unique perspective on the pharmaceutical industry. It really is this perspective that truly appreciates the value and contributions of the Hatch-Waxman Act. It also provides a perspective that makes me an advocate for a legislative process permitting the timely and efficient introduction of more affordable generic versions of biotech drugs.

The issues before this Committee today are not unlike those 20 years ago, when Congress created a legislative pathway for efficient and timely approval of generic drugs. Indeed, many of the arguments opposing Hatch-Waxman are being made and will continue to be made during this debate, namely the generic companies lack the scientific sophistication to operate in this complex arena, that it is impossible to adequately characterize the innovator products, and that the safety and efficacy of generic biotech products cannot be assured. I would like to assure you that this is not the case.

Today, I would like to make three points. First, America is at risk of losing its leadership position in biopharmaceuticals. Second, the science exists to support an abbreviated approval process. And, third, the economics for generic biopharmaceuticals are compelling, and without them consumers will lose billions in savings while citizens of other countries realize the benefits of competition.

To say that generic biotech products cannot be made flies in the face of the facts. The truth is it is already being done in other parts of the world. Biogenerics are being developed, produced and sold in countries such as Poland, China and Lithuania. The loss of a leadership position threatens that other countries will be dictating standards for regulatory approval and the quality of the products that ultimately end up in the United States. In addition, American scientists will lose the opportunity for the high-quality jobs that a robust American generic biopharmaceutical industry could bring to the United States.

The marketing of generic biotech products in other countries clearly demonstrates that products are comparable and that safety is not an issue. The exposure of thousands of patients without untoward effects demonstrates that these products are effective and safe. There are also a number of biotech products that already multi-source in the United States.

Insulin and human growth hormones are good examples. Each of these products required full development programs. A generic biopharmaceutical approval process must not require generics to recreate unnecessary clinical and pre-clinical data. The argument is made that biotech drugs are so complex that they cannot be characterized. This ignores the fact that advances over the past 20 years in analytical methods and validation techniques have allowed companies to characterize their biological drug products such that the impact of changes in processes and cell lines can be evaluated, and biologic drug products can be kept constant. The fact is that generic companies are no less capable than brand companies of apply-

ing state-of-the-art science in manufacturing and product development.

The argument is made that there is a magic process. This may have been true when manufacturing processes were not validated and analytical methods were not advanced enough to characterize the final product. This is no longer the case. If it were, many of the products made by the various biotech manufacturers would not be available today. The regulatory system allows for the flexibility needed to make the necessary changes to processes, and even cell lines, required that enables them to supply these important drug products. In reality, biotech firms routinely justify process and site changes.

Finally, the need for generic versions of biopharmaceuticals is compelling. America's pharmaceutical biotechnology industry is one of the most successful and fastest growing segments of the U.S. health care system. Ten years ago, revenues for this industry were approximately \$8 billion. According to IMS, the pharmaceutical biotech industry enjoyed in 2003 a revenue growth in excess of 22 percent, compared to 11 percent of the total market. By 2010, analysts estimate that biotechnology product sales will exceed \$60 billion.

Generic competition is essential to control costs and to continue to stimulate innovation. If Congress does not act now, Americans will continue to face escalating drug costs. We urge Congress to create legislation that will clearly define a pathway that enables FDA to review and approve generic biopharmaceutical products in a timely manner. We urge Congress to ensure that requests for FDA approval are based on science and FDA does not place requirements on generic companies to re-create already established science, thus resulting in significantly increased expense and limited access.

In summary, we recognize the investment made by the biotech industry and the need for them to recoup their investment. But as has been proven under the Hatch-Waxman Act, generic competition fuels future innovation. Now is the time to provide the balance of competition to keep America's biotech innovators strong and growing.

Thank you.

[The prepared statement of Dr. Ben-Maimon appears as a submission for the record.]

Chairman HATCH. Thank you, Doctor. We appreciate it.

Dr. Hancock, we will take your testimony now.

**STATEMENT OF WILLIAM HANCOCK, M.D., BRADSTREET
CHAIR OF BIOANALYTICAL CHEMISTRY, NORTHEASTERN
UNIVERSITY, BOSTON, MASSACHUSETTS**

Dr. HANCOCK. Chairman Hatch, I would like to thank you very much for the opportunity to appear here and to discuss these very interesting and challenging scientific issues.

At the onset, I would also like to apologize that with the short notice I had and with the complexity of the issues, I did not submit full testimony. But I am willing to update that after the hearing, if that should prove helpful.

Chairman HATCH. We will be happy to have you do that.

Dr. HANCOCK. So, now, when you introduced me, you went through some of my career. I think I have been fortunate that I have been able to experience academia and the biotechnology industry in the early days, and then the instrument companies Hewlett-Packard and ThermoElectron, because I was interested in devising new analytical instrumentation. Now, I have closed the circle and I am back in academia. So I have really seen the issue from all sides, as it were.

In this situation, I am well aware that discussing the technology can become very eye-glazing. So rather than descend into the detail, what I would like to do is just to go through some of the issues and experiences that can illustrate the complexity of biological drugs and the follow-on products.

I was actually interested to note that one of my colleagues here used aspirin as an example of a small molecule. I actually have chosen that, too, perhaps subconsciously with the thought that the complexity of this issue would leave us all with a headache. But we will see what happens.

If we compare aspirin with, say, insulin, the smallest of proteins, we see with insulin that it is a much more complex molecule and a change in a single amino acid can result in diabetes. So very subtle changes can have profound medical effects, and this is true much more so as we go to even more complex proteins. Also, we know that certain proteins are species-specific, again showing that one amino acid can make a total difference in the activity of the protein.

Then I mention the composition, that biologics can be composed of millions of atoms versus, say, 60 or 100. When I was at Genentech, we characterized Activase and we showed that Activase contained 300,000 different molecular forms. So although Activase was pure, what we were faced with was producing Activase as a constant or consistent mixture that had desirable and effective properties in the patient, but it was a very complex mixture. And that was produced in mammalian cells.

If we move on to manufacturing and product quality, obviously biotechnology is different. Rather than doing a chemical synthesis, we will take typically an insertion of DNA into bacterial or mammalian cells, and that is our manufacturing process.

Now, at Genentech we were proud that we took growth hormone and we forced *E. coli* to produce 25 percent of its protein as growth hormone. One-quarter of the cell was growth hormone. The bacteria was unhappy with that situation. It fought back. It would get rid of the excess genes, it would mutate and would try and lower the level of growth hormone expressed by reducing the number of plasmid copies. So nature does fight back, and that is true for all these engineered cells. So it requires the manufacturer to be on top of what is going on in the test tube or fermenter, as it were.

So I think as a general comment here, what we rely on is that the manufacturer puts in a lot of very good-quality science and process, and then, of course, the FDA very well regulates to check that the company is really controlling all of these things.

In the area of quality and good manufacturing practice, as an example, here I would like to note, of course, that blood is a biologic. So while we don't use blood as a raw material, many of the raw

materials to make the cell grow well are from a complex source. So there are instances of contamination. The BSE scare, mad cow disease—they remind us, then, that a natural source is not necessarily safe.

Unfortunately, we continue to discover things. We may discover new viruses, so that a raw material that we think is safe today may not be in the future. So, again, we need good science and good, I think, regulatory interactions to consistently stay on top of things.

I think we are looking at manufacturing in an international perspective. So, for example, a drug may be manufactured in Europe, and we notice that water, for example, in Europe is different from here. So I could go on with these different things, but I think the issue is that the process is very important here. We must regulate the process. We cannot just regulate through final product testing.

I also note that product variance can be recognized by the immune system in the body. So, for example, a diabetic may have some function of the pancreas. Although they have some function, they get a boost from insulin. If we have product variance, the immune system can produce antibodies to insulin and destroy the remaining pancreatic functionality. So we have actually made the patient worse rather than better. And, of course, you can have other situations where there is immune disease.

In conclusion, I would like to note, that I think there are major unresolved scientific hurdles, presently and in the near future, that are going to require very close cooperation between the manufacturers and the regulatory authorities. We are going to need animal testing and clinical trials so that at the end of the day we don't get to the situation where there is a surprise in the market.

I think ultimately if we don't do our job well—that is, in the analytical production and the testing—it is the patient population that will be the final tester and will pick up the side effects when the product is marketed. So I encourage the Committee to consider this interaction between the FDA and the manufacturers. Currently, we have a very strong process with full testing for new drug approvals. So I think as we move forward, it is important that this is not diluted, and that the science and regulation continues to be very strong.

Thank you.

[The prepared statement of Dr. Hancock appears as a submission for the record.]

Chairman HATCH. Well, thank you. I thank all of you for your testimony here today.

Let me start with you, Dr. Ben-Maimon. On average, how much will consumers save in the cost of pharmaceuticals by the presence or generic biologics?

Dr. BEN-MAIMON. I think as stated earlier, it is difficult to quantify and I think it was a very good point that was made by Dan Troy that really it depends on how many companies can enter the marketplace.

I think what is significant is when you look at the generic drug process, the savings are really reaped in two very specific areas; first, in the area of R&D, where the pathway is abbreviated enough

that the investment is more limited, and obviously then what needs to be charged at the other end can be substantially decreased.

I think the second is in the sales force. Generic companies sell essentially to pharmacies and wholesalers, whereas the brand industry promotes their products to doctors who are all over the country. Today, there are really a limited number of chain drug stores and wholesalers. So whereas a generic company can have a sales force of maybe ten sales reps, a brand company can have thousands of sales reps visiting doctors. That translates ultimately into cost savings because obviously the cost of promoting the products is less.

So I think that as the process is constructed, the savings are substantial. Even though the investment will probably be greater initially for generic companies to get into the biotechnology area, the savings will be substantial and people have estimated that the savings will be at least 50 percent. But, again, I think that depends a lot on how many other companies are out there.

I would also say, Senator Hatch, that early on it may be more expensive than as we get through the process and the systems are in place. Finally, I think it is important to note that even today Barr, for instance, is developing a vaccine for the Department of Defense. So some of the processes are already going to be in place at certain companies, and that should provide a saving to some extent as well.

Chairman HATCH. Well, you mentioned that under the current system innovator biotech companies may make changes to the manufacturing process of a biologic and establish safety and effectiveness for efficacy without conducting full-scale clinical trials by using what I think you referred to as a comparability protocol.

You suggested that manufacturing generic companies could use a similar process, namely the use of surrogate markers, under the comparability protocol to establish the safety and effectiveness of generic biologics. However, when an innovator company makes changes to the manufacturing process, they also have access to the original cell chain. Companies manufacturing generic biologics, on the other hand, do not, which seems to me a problem.

Given that the production of biologics is dependent on a number of variables, including the manufacturing process and the host cell chain, how could the producer of generic biologic ensure that the product is safe and effective, given the number of variables that differ from the production of the original biologic, without conducting new clinical trials?

Dr. BEN-MAIMON. I think it is an important point and I think it is essential to recognize that as a physician, safety and efficacy are critical. And I think the generic industry is just as committed to the safety and efficacy of its biotech products as it already is to its generic drug products.

I also think we have to differentiate between post-approval changes and pre-approval changes. When you talk about prior to approval, I think the generic industry—and I will speak for Barr, not for the generic industry, but at least at Barr we recognize that there will be some clinical trials required. Clearly, this will vary depending on the complexity of the product.

But what is submitted to the agency is a package of information and it should be reviewed and evaluated as a package. There will be multiple analytical methods, multiple assessments of the actual molecular structure and, again, comparability. And then with all likelihood, depending upon the product, there will need to be some clinical trials done, but I would venture to say that they could be done on surrogate markers such as hemoglobin, white blood cells, glucose, rather than actually trying to re-create the wheel and looking at long-term morbidity and mortality, as some of these other products were early in the development programs for the innovators.

So I think what we are asking for is a process that could be put in place that would allow us to discuss the requirements with the agency on a product-by-product basis that would look at each product as a continuum, as exists with generic drugs today. I mean, it is a continuum from the very simple to the very complex in the drug area, as well as in the biotech area. Really, the differentiation shouldn't be whether it is biotech product or a drug, but how complex that product is and what the requirements should be to ensure that it is safe and effective.

Chairman HATCH. I notice Senator Schumer is here. I will finish this question with you and then I will turn to Senator Schumer, who would like to make a statement, and then I have questions for each of the rest of you as well.

Dr. Ben-Maimon, you stated that you believe some products have been misclassified under the PHSA and that they should be rightly classified under the Food, Drug and Cosmetic Act, given that 351 of the PHSA currently speaks to the approval of biologics.

What type of products do you believe were misclassified under the PHSA, and also why do you believe that the Food, Drug and Cosmetic Act should govern the approval of biologics?

Dr. BEN-MAIMON. I am not an attorney, so I will speak as a physician reading the language in the law, which may not be the appropriate way to do things, but that is only position I can come from.

The broader of the two laws is the FD&C Act, and it is clear that at least for manufacturing requirements and GMPs and a lot of the manufacturing changes, and even now today with the merger of CBER and CDER, the FD&C is the broader of the acts and applies to—and I think it even was stated by the FDA this morning that biotech products actually qualify as drugs even though the counter may not be true.

In addition to that, when you look at the PHSA Act, it is very clear from the language that they are talking about viruses, products that induce antitoxins, products that induce immunogenicity or allergens. And then there is this term “and analogous products.”

Biotech drugs, at least the ones we are talking about today, are the products that are made through recombinant technologies, and those products really are not viruses. They are not antitoxins, they are not arsenic. They really don't meet any of the very specific definitions listed in that definition in the legislation, and they have been sort of put there under analogous products.

So I just question whether that was a convenient place to have put them rather than really where they belong, and whether they

really belong in the drug arena because they really act and perform as drugs and that FD&C regulates them as well.

Mr. BEIER. Mr. Chairman, can I comment on that question?

Chairman HATCH. Sure.

Mr. BEIER. I think the attempt to read the Public Health Service Act in that manner is frankly wrong. The FDA has construed the term "analogous" to include biotech products for more than 20 years. And to suggest an abrupt change of this nature would likely be struck down by courts as not having gone through the appropriate process. I would be glad to submit something for the record on that question.

Chairman HATCH. That would be fine. Thank you. I am going to turn to Senator Schumer for his statement and then I would like to get back to the final questions.

Senator SCHUMER. I have questions, as well, Mr. Chairman, but I will defer those until after yours.

Chairman HATCH. Okay.

**STATEMENT OF HON. CHARLES E. SCHUMER, A U.S. SENATOR
FROM THE STATE OF NEW YORK**

Senator SCHUMER. Thank you, Mr. Chairman, for holding this hearing on an issue that I care a great deal about, and many of us do, and that is affordable biologic medicines. As everyone knows, in 1984, Chairman Hatch, you authored a piece of legislation which has proven to be one of the most pro-consumer laws in our time. Hatch-Waxman helped millions of people save billions and billions of dollars on prescription drugs over the past two decades. And, of course, I have been actively involved in making it stronger.

I believe that biologics are the next frontier in our desire to make generic drugs as widely available as possible, to make cheaper drugs as widely available as possible. In recent years, we have had lots of changes, and biologics are a \$30 billion industry. They account now for 12 percent of the total of pharmaceuticals. And the industry is growing at 20 percent, so every year they increase their percentage of the drug market. This is where we should be placing our focus now.

Products with \$10 billion in sales are expected to come off patent in the next several years, and that presents a real opportunity. The bottom line is from the perspective of those of us who fought for improvements in the generic drug law, biologic medicines are no different. While the biotech industry benefitted from the patent restoration side of Hatch-Waxman, the law did not explicitly set up a fast-track generic approval system for all biologics at that time because the industry was so new. Well, it is no longer new. Patents have been extended and we ought to get to work on it. That is why I am so glad, Mr. Chairman, that you have held this hearing.

Now, obviously, there are differences between chemical drugs and biologic drugs. Biologic drugs are extremely complex and expensive to produce. Patients who use them spend tens of thousands of dollars a year for a single treatment, with the most expensive therapy costing around \$200,000. But they are critical in many instances. They are life-saving drugs treating diseases like cancer and diabetes and MS and rare diseases, and the technology holds

the promise of finding cures for things like Alzheimer's disease and Parkinson's disease.

But even more than in the chemical drug area, the exorbitant cost of the drugs often means that people can't afford to take them. Though the world of biologic medicines is an extremely complex business, we have no choice but to seize this opportunity to do the right thing for consumers, to find a way using cutting-edge science to ensure that safe, affordable alternatives are brought to market as soon as possible. Of course, we have to find a way to do this without cutting innovators off at the knees.

Companies are already marketing safe, effective and affordable biologics in Eastern Europe, Russia, Asia and Latin America. They are not yet available in the EU, which has a system of drug regulation similar to ours. But the EU has issued guidance on how biologics could be done. They issued that several years ago and they are well on their way to approving several follow-on biologic products.

So, unfortunately, in this area America lags sadly behind many other countries. Surely, if the science is adequate to produce these products elsewhere, especially in Europe where the system of regulation, as I mentioned, is similar to ours, we can do it here. So we have got to get the process rolling.

I was encouraged by what seemed to be an eagerness on the part of the FDA under Commissioner McClellan to issue a draft scientific guidance to begin to lay out what is known and what is not known about the science of producing affordable biologics. But, unfortunately, the process may be slowing.

I had some questions for the FDA. I couldn't be here. I had a conflict, but I would ask unanimous consent to submit them in writing and get them to answer them.

Chairman HATCH. We have allowed the record to be open until the end of the day.

Senator SCHUMER. So we hope the process is not slowing, but it seems it has in the FDA. Certainly, part of this process should be a vibrant public debate. But the FDA has done a whole lot of thinking on the science behind this and the agency should issue its guidance now so we can get going on the drugs we do know something about.

With biologic drugs being extremely complex, it is my understanding that there is still a full spectrum of complexity among marketed products. There are some that are easier to do and some that are harder to do, and you don't have to solve the most difficult problem before getting guidance on some of the easier problems. The FDA has said it has the authority to approve the follow-on products for those drugs that were originally approved under the Food, Drug and Cosmetic Act, and some of these drugs are less complicated on the spectrum.

We may not be able to jump head-first into this with a one-size-fits-all system that works for every drug on the market, but we have got to begin somewhere and we have got to begin now, and I hope this hearing will prod the FDA to move forward more quickly.

I thank you, Mr. Chairman, for holding the hearing.

Chairman HATCH. Thank you, Senator.

Mr. Schultz, in your testimony you refute many of the arguments made by the brand name companies that they have expressed in opposition to a system for the approval of follow-on biologics, such as that it would amount to a taking of their property without just compensation. You also state that you believe the FDA currently has the legal authority to approve generic biopharmaceuticals, and we all agree. This is one of the great strengths of this country, is the innovation in the health care industry.

How would you envision maintaining incentives for innovation in the biotechnology industry?

Mr. SCHULTZ. Well, I think the first step is to look at the incentives that are there, the patent system, and so forth. The products that are coming off patent, just roughly looking at it, have been on the market for 10, 12 or more years, and the question is: is there some problem in terms of their profitability?

I think there is a very strong case that the incentives are already there and once the products have been on the market for the period of the patent life, when the patents expire, they ought to be available for generics. Obviously, the brands are free to make a case that there are inadequate incentives, but I don't hear them making it. I don't hear them making that case.

Chairman HATCH. I will ask this series of questions to both you and Mr. Beier, if you would care to comment.

Mr. BEIER. Mr. Chairman, the existence of incentives to support risky inventions is something that you know firsthand. You know that because you were the author of orphan drug exclusivity and, working with Senator DeWine, pediatric exclusivity. So the opportunity to use market forces to create cure capital—that is, investments in start-up biotech companies—is a profound one.

The United States has 1,200 biotech companies. About 30 percent of those are publicly traded. But as I indicated before, an overwhelming majority, well over 90 percent of those companies, lose money every year. They make massive investments in R&D. The way in which their investments are protected is a combination of three things—patent protection, data exclusivity, and trade secret protection. Let me go through them in a series.

First, with respect to patent protection, as Senator Schumer noted correctly, the biotechnology industry is covered in part by Hatch-Waxman, but it is not covered with respect to process patents. And as a result, none of the patent listing or the litigation protections and procedures that were offered by Senator Schumer and Senator McCain and others last year apply to the biotechnology industry.

The second way in which the biotechnology industry has innovator rights is data exclusivity; that is, the rights they have in the case report forms and other clinical data. The question that is posed before this Committee and ultimately the whole Congress will be what are the rules with respect to that kind of data.

And then the third kind of exclusivity is trade secret protection, usually contained in the CMC section of an application to the FDA; that is the cell lines, the master cell lines, the fermentation methods, all the process quality steps that are necessary for complex proteins. That third category of information is hugely important and a subject of a lot of investment by biotech companies. So when

Mr. Schultz says it is fine when the patent expires that you can use all the data, I think that doesn't answer the complete question. You have to look at the other components, both data exclusivity and trade secret protection.

Let me also make one other point. I would like to submit for the record some rebuttal to Mr. Schultz' comments about OTC and food additives, because I don't think they are particularly apt in this case.

Chairman HATCH. Without objection, we will take that in the record.

Let me just ask both of you this question. The recent example of Pure Red Cell Aplasia, which is associated with the use of EPO, erythropoietin—is that the way you pronounce it?

Mr. SCHULTZ. EPO is good enough for me.

Chairman HATCH. EPO is good enough for me, too.

This highlighted a number of antibody-mediated reactions associated with biopharmaceuticals. The cause for this serious side effect appears to be due to a subtle change that occurs during the manufacturing and reformulation process or in the handling and distribution process. It is now clear that nearly all biopharmaceuticals induce antibodies with the possibility, as mentioned by Dr. Hancock, of these serious immune reactions by two mechanisms—the classical reaction and the new mechanism of breaking immune tolerance.

How does this risk attributed to a subtle change in the molecule due to a manufacturing or formulation change affect the issue of ensuring patient safety in the manufacture of generic biopharmaceuticals?

Mr. BEIER. Mr. Chairman, I think the best place to start is we looked at the public domain literature on manufacturing changes. It is important to make a distinction between manufacturing changes made by a company that has access to the trade secrets and the manufacturing data; that is, an innovator company making changes to their own process is quite a different thing from a follow-on company who would be necessarily using a different cell line, different fermentation, a whole series of other things.

If you look at the publicly available literature, the potential safety risks for patients include immune response that you have noted with respect to the Eprex situation in Europe, potential allergic reactions, differences in glycosylation—that is, the sugar residues around the products—and a decrease in potency.

These changes can result from either changes in manufacturing sites or methods, changes in cell lines, changes in excipients, changes in storage or in transportation, or in scale-up differences between manufacturers. All of those things need to be taken into account because for complex proteins, the FDA is regulating not just the product, but the process of manufacture.

So as the FDA proceeds with the science-based effort that they have got underway with DIA, they are going to be looking at manufacturing experts, academic experts, and we fully expect to cooperate completely with them, as we are with European regulators, in providing our best professional judgment about what is necessary to assure patient safety.

Mr. SCHULTZ. Could I comment? The FDA is charged with regulating a wide range of very, very tricky products, and everyday it is making these important scientific decisions. And this is true for the first biological to come on the market just as it will be true when the second one and the generic one comes on the market.

But this is why it is so important that in the legislation Congress give the FDA the flexibility to make the right scientific decision. And I think it is important, whether you are talking about the brand product or the generic. Dr. Ben-Maimon actually knows something about the science and she would like to comment on this as well.

Chairman HATCH. Sure.

Dr. BEN-MAIMON. I think in this situation it is exactly what I spoke about before. You have to separate post-approval changes from pre-approval changes. And in this situation, the changes that you are referring to occurred after approval and should have required additional work. They were also changes, as I understand it, in the formulation itself, with the deletion of what probably should have been considered a major component.

Quite honestly, this whole issue of the process is essential from the standpoint of the biotech industry. But the generic industry and the drug industry are actually much more experienced and much more sensitive to changes in formulation that ultimately impact things like stability. So I think when you talk about biotech generics and you are talking about pre-approval issues, you will have clinical data in the application that will have been discussed and worked out with the agency to allow you to look at the safety and efficacy of the product at the time of approval.

What occurs post-approval is dictated by all kinds of regulations with prior approval, and you have heard in some of the testimony that was written changes being affected and some others. But, clearly, prior to approval, whatever the development process is will be tested clinically in patients. So the agency will be basing its decision not on changes, but on the data contained in the application, which is dramatically distinct from the Eprex circumstances which happened post-approval.

Chairman HATCH. Dr. Hancock.

Dr. HANCOCK. I have a concern that this discussion makes it sound easier than it really is. The changes are so subtle that I think often, even within the company, one cannot quite understand what happened to the product when a particular resin or purification or whatever changed. So I just want to emphasize for the Committee that these changes are very subtle and very wide-reaching, and we need to be very careful as we move forward.

Chairman HATCH. Thank you all. I appreciate you. I have a number of questions I am going to submit in writing because this is a complex area, and I would appreciate your sending back your answers as quickly as possible. My time is up.

Senator Schumer, I have got to leave in about 5 minutes.

Senator SCHUMER. I will be quick, Mr. Chairman. I would first ask unanimous consent to submit a whole lot of questions in writing.

Chairman HATCH. Without objection.

Senator SCHUMER. For Mr. Schultz, again, it is my understanding that the FDA had planned to issue draft guidance this summer laying out the scientific parameters relevant to the creation of follow-on biologics. Is that correct?

Mr. SCHULTZ. It was widely anticipated. That was my understanding, too.

Senator SCHUMER. Right, okay. Now, it seems this guidance is being delayed and they are having this public symposium first. At least it seems to me that the FDA has tremendous scientific expertise here. They have already said they have authority to approve follow-up products, at least for some of the drugs.

Wouldn't it make sense from your point of view and from the consumer's point of view for the FDA to issue its guidance now so we can get going on products we know something about?

Mr. SCHULTZ. Particularly since the guidance that it was going to issue was a draft for comment. That is, it was going to be its first cut at it and there would have been a public discussion anyway. Now, I gather that is all being pushed back for a symposium.

Senator SCHUMER. The public discussion doesn't have a root, a basis. It sort of floats out there in the ether, I guess. Do you have any idea why they delayed it?

Mr. SCHULTZ. No, I don't.

Senator SCHUMER. Does anyone here?

No, okay.

Does anyone disagree that the FDA should move forward now? I am sure there would be some people maybe at the ends of the table.

Dr. HANCOCK. I will take the bait, Senator. I do represent the coast; maybe it is the end of the table, too. I participated in the first consensus forum meeting the FDA held right at the beginning of biotechnology, which related to the approval of insulin. And I really think it is a very good process. It brought together all of the various biotech companies in the world at the time and international experts, and I think drove a consensus together. I really think that did speed up the FDA.

I can understand your concern for not having further delay, but I think the best way to speed things up is to hold this meeting quickly and for the FDA then to pass its comments on to you. I would really support that process.

Senator SCHUMER. But what would be wrong with doing it the inverse, as Mr. Schultz sort of alluded to—put out their guidance first, then have the big discussion, because they are going to have to have comments anyway?

Mr. BEIER. Senator, I think the advantage to having a public forum before the issuance of a draft guidance is seen by the fact that the FDA frequently adopts that particular point of view. I would be glad to submit for the record the ten or more instances in which they have done this in the last 10 years.

The most recent one was the issuance of a draft guidance on pharmacogenomics, an equally complicated scientific endeavor—the opportunity for targeted medicine like Gleevec and other things that we all celebrate everyday that bring cures to people with cancer. The development of this targeted therapy is of huge public health consequence. But before issuing the draft guidance, the FDA

had several public forums, laid out all the appropriate scientific issues. As a result, when they finally came out with a document, it was more robust and there was a greater consensus.

In the long run, consumers benefit by having confidence that the agency has engaged in a science-based, transparent public process, not just that several people in Rockville or elsewhere have thought about something and issued draft guidance.

Senator SCHUMER. Mr. Beier, no one is disputing that. The question is whether they could have issued the guidance and then had some discussion based on it and then reacted to what the public had to say.

Mr. BEIER. The example, Senator, is if you look at what has happened in the European Union, the European Medicines Evaluation Agency came up with guidance in December. The agency is now struggling, because they did not have a public forum, did not bring in experts, about what exactly it means on a particular product basis. So an incomplete record can produce either unintended consequences or can place patients in a situation where they may lack confidence in the appropriate regulatory authority.

Senator SCHUMER. Mr. Schultz.

Mr. SCHULTZ. There is a famous quote from Samuel Jonson, "nothing focuses the mind like a hanging." Well, nothing focuses the FDA like a directive from Congress. This where we are in the early 1980's. The FDA was talking about an ANDA program. It would have been many, many years before it got there if it weren't for the 1984 Hatch-Waxman Act. This is where they were in the late 1980's with regard to nutrition labeling. There again, Congress stepped in and it got done. I personally believe that this issue demands Congressional attention if your desire is to get it done.

Senator SCHUMER. I agree with you completely, Mr. Schultz and I am going to focus on this and push the FDA to move forward because I agree. Sometimes, not always—and who knows in this case—having all these forums without anything concrete just leads to more forums and takes too long a time. I don't see the contradiction in having guidance and then having discussion and still solving the problems that Mr. Beier mentioned.

You can get the last word from my questions, Dr. Hancock, because I am always mindful of my Chairman's schedule.

Chairman HATCH. He is never mindful of my schedule, never, not once in the whole time he has been on this Committee.

Senator SCHUMER. That is one of the nicest things he has said about me in quite a while.

[Laughter.]

Chairman HATCH. Actually, I have said one or two other nice things about you.

Senator SCHUMER. Yes, you have; yes, you have, Mr. Chairman.

Chairman HATCH. Actually, I appreciate my colleague. He is a very thoughtful, very aggressive, very hard-working colleague, and I appreciate him.

Senator SCHUMER. Dr. Hancock.

Dr. HANCOCK. I realize that I am between the Committee and lunch, so I would agree that Congress should really push all of us to be very vigorous in this area. I support that a hundred percent,

but I would encourage you to give the FDA access to the international body of science. These are very difficult issues.

I am actually working with the Human Proteom Organization, and it is amazing when you have a group of international scientists together what they come up with. I think we would move faster by assisting the FDA with as much outside help as we can, and I think the academics and government scientists stand ready to do that.

Thank you for the last word.

Chairman HATCH. Well, thank you. Let me just say, Mr. Schultz, I agree with you. It is inevitable that there will be legislation with regard to follow-on biologics. It is my hope that this hearing today will be a help to build a solid foundation so that we can do the job here, and it will be wisely done, in developing that legislation. In that regard, I would ask each of you and others in the audience as well and those who watch this on television to give us the best ideas you can so that we can proceed and get this all done.

Finally, I just had one more question for you, Mr. Beier, that struck me as something I should ask before we finish, and this will be the last question. You stated in your submitted testimony that follow-on biologics cannot be considered therapeutically equivalent to the innovator product.

How do you reconcile that argument with the 1995 FDA decision or finding—I guess it was a finding regarding Avanex, which was a biogen product for the treatment of relapsing forms of multiple sclerosis, that two cell's lines could be unique and yet comparable? This is the way I interpreted that.

Mr. BEIER. The testimony that I submitted indicates that we believe that follow-on products should not be therapeutically substitutable, which is you shouldn't have a patient on one particular product and then switch it to a follow-on product because that may produce a different immune response. So that is the answer to your first question.

With respect to the specific case that you are talking about, it is a very highly unusual fact pattern involving an American company and a German company who collaborated who had a contract. Both companies had access to trade secret information and manufacturing data. The two companies then had a business disagreement and the submission of data from one of the dissatisfied parties did rely on the data from the other company, but there had been previous access to this information. So I think it is a relatively unique set of circumstances that led to that particular approval.

Chairman HATCH. Well, thank you. I appreciate your comments on that. We will submit some further questions in writing. I think this has been a very interesting hearing.

I am sorry, Dr. Hancock, that I ran out of time. I had some questions for you, as well, but I will submit them in writing and I know that you will more than adequately answer them.

We are very grateful to all of you. We have learned a lot here today, and we challenge all of you and others in the scientific community to help us with regard to what I propose will be follow-on legislation. Thanks so much.

With that, we will recess until further notice.

[Whereupon, at 12:23 p.m., the Committee was adjourned.]
[Questions and answers and submissions for the record follow.]
[Additional material is being retained in the Committee files.]

QUESTIONS AND ANSWERS



**Responses to Questions from
Members of the Senate Committee on the Judiciary
Regarding "The Law of Biologic Medicine"**

July 30, 2004

Questions from Senator Hatch

1. *Mr. Beier, you stated in your submitted testimony that "follow-on biologics cannot be considered therapeutically equivalent to the innovator product." However, how do you reconcile this argument with the 1995 FDA finding regarding Avonex, a Biogen product for the treatment of relapsing forms of multiple-sclerosis, that two cell lines could be unique and comparable?*

Only if one sponsor's product is determined to be "therapeutically equivalent" (TE) to another, may one be substituted for the other with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. *See Approved Drug Products with Therapeutic Equivalence Evaluations* (24th ed.) (also known as *The Orange Book*) at section 1.2. As noted in our written testimony to the Committee (June 23, 2004), and explained below, we believe that two biological products cannot be considered therapeutically equivalent. Thus, to the extent that many state and federal health care systems rely on FDA's TE ratings to allow for mandatory or permissive substitution, follow-on biologics could not be substituted for the pioneer.

Two drug products, manufactured by different sponsors, are considered to be “therapeutically equivalent” only if they are “pharmaceutically equivalent,” “bioequivalent,” and manufactured in accordance with good manufacturing practice standards. *See* Preface to *The Orange Book*. A pharmaceutically equivalent drug product must be shown to contain identical amounts of the identical active ingredient in the identical dosage form. 21 CFR 320.1(c). The active ingredients in two equivalent products must also be shown to meet identical standards of identity, strength, quality, purity, and potency (*see id.*), and must be shown to have the same rate and extent of absorption in the body. 21 CFR 320.1(e). As discussed in our written testimony, this standard cannot be met for biological products.

In the case of Avonex[®] (interferon beta-1a), Biogen was one of the original sponsors of an earlier version of interferon beta, known as “BG9015.” As such, Biogen had access to proprietary information and scientific knowledge about the product. Specifically, Biogen, along with its joint venture partner -- Rentschler Arzneimittel GmbH & Co. -- developed and manufactured BG9015 and sponsored the pre-clinical and clinical studies of the substance. When Biogen later sought approval for Avonex[®], it did so by showing comparability to BG9015, and it did so with rights to the pre-clinical and clinical data that had been generated for BG9015, as well as to the chemistry, manufacturing, and control information relevant to that product’s creation and manufacture. This type of proprietary information and scientific knowledge about the product would not have been available to another

manufacturer; thus, the Biogen example is not analogous to that of a “generic” manufacturer seeking approval of a follow-on biologic.

2. *Mr. Beier, you referred to the Orphan Drug Act of 1983 as “the best example” of how Congress can encourage innovation and competition. Specifically, you referred to the provision in the Orphan Drug Act that provides for a seven-year period of market exclusivity after approval. Would the grant of a period of market exclusivity preserve the incentive for biotech companies to continue innovative research and development of new biologics? If not, what provisions would preserve the incentive for innovation?*

We believe the Orphan Drug Act provides an illustration of how Congress can stimulate investment and innovation to address a particular problem. The use of a seven-year market exclusivity period has proven to be a significant incentive to manufacturers to develop new products for use in treating rare "orphan" diseases and conditions.^{1/} When properly implemented, it protects the pioneer sponsor from competition within the orphan population for seven years. Its value, however, is greatly diminished if "therapeutically equivalent" generic products can be substituted for the pioneer product during the seven-year period -- a phenomenon that is becoming more common.^{2/}

We point this out to show that each scenario requires its own set of incentives, along with careful oversight of the actual application of the legislation. Whether any particular incentive proves to be valuable will depend to a large extent on how

^{1/} See Carol Rados, *Orphan Products: Hope for People with Rare Diseases*, FDA Consumer (Nov.-Dec. 2003) ("Since 1983, the ODA has resulted in the development of nearly 250 orphan drugs, which now are available to treat a potential patient population of more than 12 million Americans.")

^{2/} See, e.g., *Sigma-Tau Pharm., Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002) (upholding FDA's approval of generic versions of a drug for a use no longer covered by seven-year period of orphan exclusivity, although use of the drug for a different condition was still subject to exclusivity).

it is implemented and whether substitutable products will be allowed to enter a protected market during the statutory exclusivity period.

Last, we note that the use of market exclusivity periods should be viewed as one component of a comprehensive system that preserves and creates incentives for innovation in the biotechnology industry. Other measures include strong patent and trade secret protection, patent term restoration, data exclusivity rights, a transparent and predictable regulatory environment, and an efficient review and approval process.

3. *Mr. Beier, you have stated that if Congress establishes guidelines for the approval of follow-on biologics, they need to ensure that innovator trade secrets submitted to the FDA are protected, such as the manufacturing process of a pioneer biologic. However, if an approval process for generic biologics is developed, it is generally believed that the FDA will have to refer to the information submitted to the FDA by the innovator company to establish whether a proposed generic is sufficiently similar to a pioneer. I think we all recognize that the FDA would not release this information to the general public. Rather it would only be used by the FDA for purposes of reviewing an application for approval. Given this protection, do you feel additional protections should be provided to innovator companies?*

It is not clear from the question what is contemplated by having FDA “refer to the information” submitted by one sponsor to determine if another sponsor’s product is “sufficiently similar.” In general, we believe that the use of proprietary data to approve follow-on or competitor products will destroy the incentive necessary to sustain high-risk investment in new drug development. It would not be acceptable, for example, for FDA to disclose proprietary manufacturing information to a follow-on applicant, or even to suggest such information to an applicant by deeming an application deficient for failing to include assays or

processes that originate in the pioneer's application. Trade secrets relating to manufacturing methods and processes are of particular importance for biological products, because the manufacturing process is essential to the identity, purity, and potency of these products.

We also believe that pre-clinical and clinical data developed by the pioneer, and not otherwise in the public domain, cannot be incorporated by reference to make an otherwise deficient follow-on application sufficient. This is effectively no different than releasing such data to the public. Such information represents the core of innovator research and development investment, and to appropriate it or reference it to approve another sponsor's product would substantially erode the incentive to develop such data.

4. *Mr. Beier, if you could expand for a moment on one of your statements. You stated that a follow-on approval system should allow for a case-by-case pre-market comment period on the standards for specific categories. Could you explain what you mean by a pre-market comment period? Specifically, are you requesting that a comment period be available each time FDA considers the application for a generic biologic – which would be a case-by-case comment period? Or, are you requesting that there be a comment period for each specific category of biologics, such as pulmonary, cardiovascular, and the like – which would be a comment period for a category of biologic?*

In short, we believe that any future follow-on approval system should include a pre-market public process for obtaining technical input from the pioneer sponsor and the innovative industry, as well as medical and scientific input from healthcare professionals and patients.

We expect that follow-on biologics will raise novel and complex scientific issues, in which one sponsor's version of a macromolecule product will be compared

with another person's version. To date, such products have been considered to have unique safety and efficacy profiles. A follow-on system will require new inquiries into the extent to which such products may be considered the same, such that a follow-on sponsor may forgo certain testing, with no loss in patient safety or efficacy. Because we believe such analyses will be protein-specific, the process we envision will likely require product-specific input from the pioneer (and other stakeholders, including healthcare professionals and patients), rather than category-specific input. For example, it is unlikely that categorizing and analyzing products by therapeutic class will be productive because of the variety of protein structures that are likely to be found within a therapeutic class. Unlike small molecule drugs, where equivalence issues often relate to the release of the active ingredient from the dosage form (*e.g.*, topical, inhaled, and ophthalmic drug products), the issues with follow-on biologics are, foremost, likely to relate to the specific protein.

Pioneer sponsors, who have vast experience with these proteins, should be provided the opportunity to participate in the development of testing standards that will inform the review of follow-on products. This should be achieved through a product-specific, pre-market process in which FDA also receives input from the scientific and medical communities, patients, and other interested persons.

5. *One of the areas of disagreement in the area of biopharmaceuticals is in the proper terminology for their generic products. The brand name companies abhor generic biologics, and suggest follow-on biologicals; in your testimony you state that the generic industry prefers "generic biopharmaceuticals." The Europeans propose using off-patent biotechnological products (OPBPs) for describing such products. Would that be an acceptable terminology?*

It appears this question may have been intended for William Schultz and the Generic Pharmaceutical Association. Nonetheless, we will provide our perspective.

We believe the term “generic” does not apply to biological products. As described in our written testimony to the Committee, the term “generic” implies a degree of sameness and interchangeability between the follow-on and the pioneer that cannot be established for biological products. (This principle has been recognized in the European Union (EU), where follow-on products are called “biosimilar” medicines.) Amgen also objects to the phrase “off-patent biotechnological products,” because it is imprecise and potentially misleading; the patent and exclusivity estate for a given product may change over time, with new patents and exclusivities being added as novel processes and uses are developed for existing products. Instead, we believe the term “follow-on biological products” or the short-hand “follow-on biologics” is the least objectionable option in use today.

Questions from Senator Leahy

1. *A recent article, "Combating Generics," described strategies that companies might employ to fend off competition from generic rivals. One strategy mentioned in the article was "evergreening" – the practice of preempting generic entrants with new, improved versions of branded drugs before their patents expire. To some extent it would seem that such strategies limit innovation when compared to a fast-track system for generic biologics. Do you agree that fast-track systems might spur innovation by encouraging pioneer companies to continue to develop new therapies in order to compete in the marketplace?*

We do not have access to the article referenced in the question ^{3/}, but we surmise that it relates to small-molecule drug products and the approval of generic versions of such products under the Hatch-Waxman Act.

As you suggest in the question, one theory behind a robust generic drug approval program is that it will spur pioneer sponsors to continue to develop new therapies to replace those that have been captured by generic sponsors. There is evidence, however, to suggest the opposite -- that a robust generic system causes pioneers to be much more conservative or selective with respect to investing in new therapies. ^{4/} That is, pioneers may take fewer large-scale risks in the face of potential generic competition and, instead, focus on making incremental changes to

^{3/} This article is not available publicly.

^{4/} See, e.g., Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* at 37-50 (July 1998); Laurie McGinley, *Survey of FDA Approvals Questions Patent Extensions and Fuels Industry Feud*, WALL STREET JOURNAL (May 29, 2002) (citing paper by National Institute for Health Care Management, *Changing Patterns of Pharmaceutical Innovation*, May 2002, available at <http://www.nihcm.org/innovations.pdf>).

proven therapies. The article described in your question would appear to support this point.

We believe this issue, as applied to biotechnology products, requires careful study. As expressed in our written testimony to the Committee (June 23, 2004), we remain deeply concerned about the potential for an ill-conceived follow-on system to destabilize the venture-based investment model that has driven the biotechnology revolution.

2. *In your testimony you noted the European Union's recently-passed "pharmaceutical review" legislation and characterized the EU approach as a careful balance between the rights of innovator companies and follow-on companies. However, you also mentioned the United States' robust trade secret protections, which seem to place hurdles in the way of efforts to create a fast-track generic biologic approval process. Do you believe it is possible to develop a variation of the European Union approach that would mesh with American trade secret laws?*

Among other broader initiatives, the new European Union (EU) pharmaceutical review legislation codified and expanded upon earlier EU regulations and directives. The new law provides a basic legal framework for the approval of follow-on biologics, known in the EU as "biosimilar medicinal products." The new law also harmonizes across the EU the period for protection of data contained in innovator product applications, often referred to as an "8+2+1" system. The "8+2+1" system provides that follow-on applicants are barred from filing an application with the European Medicines Agency (EMA) for an eight-year period following the approval of the innovator product. Follow-on products may not be placed on the EU market for an additional two years. Lastly, a possible one-year

extension of data exclusivity is available for the innovator product if a new therapeutic indication of the product is approved during the first eight-year period. Because the "8+2+1" system of data protection applies without prejudice to existing laws that protect proprietary information, however, it is unclear to what extent follow-on applicants may be able to reference innovator's trade secrets even after the lapse of the data exclusivity period.

For example, in the EU, trade secrets are protected at both the member state and EU levels. National laws generally treat product formulation and method and process information as trade secrets. At the EU level, a regulation provides protection of trade secrets contained in applications for medicinal products. See *Council Regulation 2309/93, 1993 O.J. (L 214) 138*. Furthermore, the European Communities (EC), like the United States and other World Trade Organization members, is subject to Article 39.3. of the *WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)*. This provision mandates that "[u]ndisclosed test or other data, acquired as a condition to marketing approval of pharmaceuticals, the origination of which involves a considerable effort, shall be protected against unfair commercial use." Such trade secret protections are particularly crucial in the context of biological products, to the extent trade secrets relate to manufacturing processes, because those processes are essential to the identity, purity, and potency of biologics.

Whether the nascent EU approach to the approval of follow-on products is a suitable model for the United States remains to be seen. To the extent the EU approach is based on any type of disclosure of what would be recognized as trade secrets in the U.S., we do not believe it could serve as a model for this country. Robust trade secret protection is a fundamental cornerstone of the innovation-driven American biotechnology industry, and it must be maintained. However, to the extent the new EU legislation provides comparable trade secret protection and provides for data protection of critical information contained in innovator applications, it may provide useful lessons. As the EU approach continues to develop, we would support further study of whether it includes ideas that could be integrated into our own approach to follow-on biologics.

Questions from Senator Durbin

1. *How has the European Union addressed the issue of generic biologics? What problems have they faced in their approval process for generic biologics?*

As part of the broader “pharmaceutical review” legislation^{5/}, the European Union (EU) recently established a basic legal framework for the approval of follow-on biologics, known in the EU as “biosimilar medicinal products.” The new law makes a clear distinction between biological products and small-molecule, chemically-derived products. Since it is not currently possible to determine that two biological medicinal products are identical, the presumption of the new law and related guidelines is that the approval of biosimilar medicinal products invariably will require original pre-clinical and clinical studies for each proposed indication. It is not sufficient to cross-reference studies conducted on the reference innovator product and merely show bioequivalence with that product. Furthermore, the new EU legislation, as well as the *World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)*, prohibits or substantially limits the use of proprietary innovator data to support the approval of biosimilar products.

^{5/} This new legislation also harmonizes across the EU the period for protection of data contained in innovator product applications, often referred to as the “8+2+1” system. This system bars follow-on applicants from filing an application with the European Medicines Agency (EMA) for an eight-year period following the approval of the innovator product. Follow-on products may not be placed on the EU market for an additional two years. Lastly, a possible one-year extension of data exclusivity is available for the innovator product if a new therapeutic indication for the product is approved during the first eight-year period.

Notably, however, the legislation does not specify the type and amount of original clinical data that sponsors of follow-on products will have to provide. This will be determined by the European Medicines Agency (EMA) on a case-by-case basis in accordance with relevant scientific principles and guidelines. It seems likely that substantial additional guidance documents will be needed before the EU can begin to approve any follow-on biologics. Furthermore, the EMA (like FDA) will need to determine whether additional data requirements will be specified for follow-on biologics on a product-specific or class-specific basis.

The EMA should establish a public process to govern the establishment of these additional requirements, and determine to what extent pioneer manufacturers and other parties will be included in that process. Transparency in the process and full participation by affected stakeholders is needed to ensure outcomes that benefit patients and are clinically sound.

2. *Do you take the position that there is absolutely no biopharmaceutical that can give rise to a follow-on version as a therapeutic equivalent? Even if you believe that that is currently the case, do you believe that it is impossible to develop scientific solutions that would in fact make such follow-on products possible with respect to at least some biopharmaceutical products?*

To the extent you are asking whether therapeutic equivalence can be established for follow-on biological products, we note that two drug products, manufactured by different sponsors, are considered to be “therapeutically equivalent” only if they are “pharmaceutically equivalent,” “bioequivalent,” and manufactured in accordance with good manufacturing practice standards. *See Preface to Approved Drug Products with Therapeutic Equivalence Evaluations (24th*

ed.) (also known as *The Orange Book*). A pharmaceutically equivalent drug product must be shown to contain identical amounts of the identical active ingredient in the identical dosage form. 21 CFR 320.1(c). The active ingredients in two equivalent products must also be shown to meet identical standards of identity, strength, quality, purity, and potency (*see id.*), and must be shown to have the same rate and extent of absorption in the body. 21 CFR 320.1(e). If one sponsor's product is determined to be "therapeutically equivalent" to another, then the two products may -- according to FDA -- be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. *See The Orange Book* at section 1.2. As discussed in our written testimony to the Committee (June 23, 2004), we do not believe this standard can be met for biological products.

Among other things, it is currently not possible to characterize therapeutic proteins as thoroughly as we can characterize small-molecules. This inability to fully characterize proteins, coupled with a lack of understanding of what could cause a protein to be immunogenic, limits the ability of regulatory bodies to determine if a follow-on biologic is as safe as the innovator product. It is impossible to speculate on future scientific advances that could allow a more thorough characterization of a protein or could allow reliable prediction of immunogenicity. Currently, however, we believe that immunogenicity cannot be adequately assessed without clinical studies. We also expect that differences in cell lines and

manufacturing processes will always result in inherent, clinically relevant differences between products.

3. *What are your recommendations for a regulatory pathway that would balance the public interest to lower healthcare costs with innovators' proprietary rights?*

We believe that patients deserve the best and safest medicines that technology can deliver, at the most competitive prices. To achieve both of these important goals, however, will require delicate balancing.

For example, to ensure that the newest and best therapies continue to be developed by biotechnology companies, any process developed by Congress regarding follow-on biologics must protect incentives for innovation. This is particularly crucial when it comes to the field of biotechnology, which is in its infancy compared to the traditional small-molecule drug market, and is vulnerable to market instabilities. It will be important to maintain an incentive structure that promotes investment in research and development. This begins with strong protection of intellectual property, including new compositions and processes, as well as clinical and manufacturing data. Depending on the specific provisions eventually enacted by Congress, other meaningful protections, such as marketing exclusivity periods, are also warranted to support continued innovation.

As to the potential approval pathway for any future follow-on product, and the requirements guiding the review of any such products, these must be developed through a structured, public process. FDA and the biotechnology, science, and medical communities must first resolve the scientific issues implicated by follow-on

products, including questions of characterization and comparability. The regulatory development process must be transparent, predictable, and science-based, and must allow for a case-by-case premarket public process regarding the standards for specific products.

As to the specific requirements that any potential follow-on product must meet, these must be guided first and foremost by patient safety. With this in mind, we believe that it is premature to consider a true generic approval process for follow-on biologics (akin to the Hatch-Waxman pathway for generic drugs). As the science develops, there may be opportunities to alter certain of the requirements (although not with respect to safety or manufacturing-related data) for follow-on products. Even then, follow-on products must be held to the same high standards of safety, efficacy, quality, and manufacturing requirements as innovator products. For example, pre-clinical and clinical data must be provided by the follow-on company in the pre-approval stage, and the data should establish the immunogenicity of the proposed product. Post-marketing safety commitments also will be necessary to ensure the continued safety of any proposed follow-on products.

Questions from Senator Schumer

1. *You have expressed concern that generic companies lack the scientific and manufacturing expertise to produce follow-on biologics. Do you agree that there are some products which are less complicated, and for which the science may be adequate to allow for follow-on products? Would you be opposed to Congress codifying FDA's authority to approve follow-on products if we leave it to the Agency to decide if and when the science is adequate?*

To be clear, the issue is not whether today's generic drug companies have or do not have the technical expertise to produce follow-on biologics. The issue is whether any firm, starting with its own unique cell line and means of production, can produce a protein that could be considered identical to and substitutable for another firm's version of the protein.

Even for relatively "less complicated" products, there will be inherent differences between the innovator and follow-on products because each will be derived from a unique cell line and an original manufacturing process. The same type of cells (e.g., Chinese Hamster Ovary cells or *E. coli* cells) often respond differently to fermentation, purification, and other steps in the production process, such that the final products made from similar sources will vary. Furthermore, biological products cannot be fully characterized, in the same way or to the same extent that small molecule drugs can be characterized. Thus, a meaningful comparison between a pioneer and a follow-on product -- just to establish the sameness of the active ingredients -- requires clinical testing. It would be impossible to determine, without original clinical trials, if the innovator and follow-on products would have the same therapeutic affect and safety profile in humans.

We believe the scientific issues surrounding follow-on products should be publicly debated and resolved before Congress acts to establish an approval pathway for those products. As the European experience has shown, acting in the reverse order may not bring safe and effective therapies to consumers any more quickly and, in fact, may raise more questions than it solves.

2. *While Amgen says that FDA has never approved a biologic under an abbreviated process, is it my understanding that FDA has approved biologic products with less testing than was required for the first product in a given class. Do you know if that is in fact the case? Do you believe that the agency had the right to approve these additional products requiring less data? Does it constitute a "takings" or did the Agency's knowledge of the product type allow it to require less data?*

It is reasonable for FDA to calibrate the clinical testing requirements to the specific product under review, requiring quantitatively less or qualitatively different testing in some cases based on what is already publicly known about the therapy. See, e.g., Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998) (noting that, in certain cases, "FDA has relied on only a single adequate and well-controlled efficacy study to support approval"). It is inappropriate, however, for the agency to use proprietary data from one sponsor's application to approve the application of a different sponsor. Such data constitute property protected by the Fifth Amendment and, thus, may not be taken without just compensation.

3. *If a brand company makes changes to its product – changes in the process or method by which it is produced – is that company required to repeat its clinical safety and efficacy studies to prove the product is the same?*

A demonstration of "comparability," following a process or methodological change, is inherently fact specific. FDA has provided extensive guidance to sponsors regarding the design of comparability protocols under a variety of scenarios. *See, e.g.,* Guidance for Industry, *Comparability Protocols, Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information* (Sept. 2003). As a general matter, and to analogize to the follow-on context: It is our expectation that a biotechnology sponsor who concurrently proposes to change cell lines, adopt a new production process, and move to a new manufacturing facility, would be expected to generate some amount of clinical data to support a finding of comparability.

4. *In your testimony, you recount problems which arose following manufacturing changes made by Johnson & Johnson to a product called Eprex, a product made using technology licensed from Amgen. Specifically, you said that as a result of manufacturing changes, more than 160 Eprex patients have experienced adverse events as a result of their bodies' response to the product. This is certainly disconcerting, but since you seem to offer this as an example of why follow-on versions of biologics should not be approved without substantial clinical trials, I am wondering whether in this case clinical trials would have even been able to identify the adverse event. How many people took the J&J product in all? If J&J had done full clinical safety and efficacy trials (similar to the size of Amgen's) after making the manufacturing changes and before putting that version of the product on the market, would that adverse event, statistically-speaking, definitely have been identified in the clinical trials, or was its occurrence of a magnitude that would not have been picked up in such trials?*

There have been 180 reported cases of antibody-mediated Pure Red Cell Aplasia (PRCA) associated with Eprex[®]^{6/}; the true incidence is unknown and may be higher. The overwhelming majority of these reports have been associated temporally with certain changes in the manufacturing of Eprex[®]. Whether this adverse event could have been anticipated, with a thorough pre-clinical and clinical safety program, is speculative and depends, in part, on an intimate knowledge of the nature and extent of the changes that were made to the process and the product.

That said, an appropriately designed and reasonably sized clinical study program can support a conclusion that a biological product will not have a high rate of immunogenicity and importantly, will not have a high rate of neutralizing antibodies. Such a study can identify a specific immune response or may provide signals that suggest a specific safety risk or, at a minimum, suggest the need for more study. Last, depending on the extent of the manufacturing changes, and information developed in the clinic, it may have been appropriate to do a post-market follow-up study to add to the database and, again, increase the likelihood of identifying a rare or unexpected risk.

Importantly, the experience with antibody-mediated PRCA demonstrates the complexity of biological products. It shows that even sponsors, who possess all of the proprietary manufacturing and clinical data for a given product, may make changes to a product that could potentially result in rare, but serious, safety issues.

^{6/} See Johnson & Johnson Pharmaceutical Research and Development, Company News, Summary of PRCA Case Reports, at <http://www.jnjpharmarnd.com/company/news.html>.

5. *When Amgen makes changes to its product, it can compare the new production process to the original process. You argue that it is impossible for a generic manufacturer to reverse engineer a biologic and show safety and efficacy based on something other than trade secret data. How do you know this is impossible? Is it a method Amgen has ever attempted?*

We have studied a large number of process changes for our marketed and development products. Many changes have not been implemented because of differences in process parameters that were unacceptable, differences in product quality values that met specifications but were out of trend from our historical experience, and differences in product quality parameters that were not specifications but were detected using proprietary methods and in-house reference standards. In addition, published data have shown that when companies attempt to duplicate a widely-used biotechnology product such as epoetin, there are significant differences in the resulting products that could affect safety and efficacy. See, e.g., Huub Schellekens, M.D., Ph.D., *Biosimilar epoetins: how similar are they?*, *EJHP* [Official Journal of the European Association of Hospital Pharmacists] (March 2004) (attached).

Response of Dr. Carole Ben-Maimon, President and Chief Executive Officer, Barr Research, Inc., to Questions Submitted as Follow-up to Senate Judiciary Committee Hearing, "The Law of Biologic Medicine" (June 23, 2004)

QUESTIONS SUBMITTED BY SENATOR LEAHY

1. Biogenerics are being developed, produced and sold in countries such as Poland, China, and Lithuania. Based on this developing international industry, you expressed the fear that the United States will lose its preeminence in this field. However, while you noted the risks of Congressional inaction, others have cautioned against creating a fast-track approval process because of the potential health risks associated with generic biologics. Given the conflicting testimony, how do you weigh the risks and competing interests? Are there other mechanisms available to reduce the cost of prescription innovator biologics?

Response: The Food and Drug Administration's foremost consideration must be the safety and efficacy of new drug products, and this principle similarly applies to generic biopharmaceutical products. FDA is the expert agency that Congress has charged with making decisions about drug safety and efficacy and, of course, it should continue to have that responsibility. Today there are several biologics that are good candidates for generic competition, including but not limited to human growth hormone and insulin. It is our understanding that the scientists at FDA have concluded, as we have concluded, that generic versions of these products could be approved with limited additional testing to assure safety and efficacy. FDA, however, is delaying implementation of a regulatory program for approval of these products because of uncertainty about the appropriate policy for generic biopharmaceuticals and uncertainty about its legal authority. Unless Congress gives the agency clear direction, this uncertainty will act as a severe disincentive to the industry to develop generic biopharmaceuticals for sale in the United States, thus preventing the availability of more affordable biopharmaceuticals.

In other words, Senator Leahy, we are not advocating that FDA's standards for safety and efficacy be lowered to allow generic biologics on the market. Instead, we are urging that Congress give FDA the authority to eliminate unnecessary requirements to allow those products to enter the market once manufacturers demonstrate that they can meet the stringent safety and efficacy standards that FDA sets for these products. Of course, all current patent and intellectual property protections would continue to apply.

There may be other mechanisms to reduce the costs of innovator prescription drugs. Yet, the experience with chemical drugs demonstrates that competition from generic versions will be essential to any successful effort to reduce costs to consumers and healthcare providers, and to stimulate continued innovation.

2. You mentioned that other countries are in the process of approving, or have already approved, "follow-on" biologics. How did these countries resolve the dilemma that we now face in approving these potentially lower-cost biologic therapies?

Response: As indicated in response to question 1, we do not believe that there is a dilemma. Instead, the issue facing Congress is whether it should confirm that FDA has the authority to eliminate testing and data requirements that are not necessary in order for the generic version of a biologic to satisfy the safety and efficacy standards under current law. For decades, the United States has been a world leader in many critical areas of drug development, and we believe that we can make important strides forward in the area of generic biopharmaceuticals. However, it is critical that we do so in a way that does not compromise the high safety and efficacy standards that Americans have come to expect. With help from Congress, we strongly believe that FDA can build a regulatory program that ensures safe and effective biopharmaceuticals at competitive prices.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

1. You stated in your testimony that "[t]he marketing of generic biotech products in other countries clearly demonstrates that the products are comparable and that safety is not an issue." Your comment suggest that the safety and efficacy of follow-on biologics are determined by patient use rather than by pre-market scientific evaluation. Shouldn't safety and efficacy of follow on biologics be evaluated through a specific regulation pathway based on the standard three stage clinical trial format?

- a.) How many follow-on biologics have been developed and used in Asia and in Eastern Europe?
- b.) What is the adverse event history and what are the legal implications for these follow on biologics?

Response: Senator Durbin, we agree that the safety and efficacy of generic biopharmaceutical products should be determined by scientific evidence. As the level of experience with these products and number of patients exposed to these products increases, it becomes unnecessary to repeat studies that will not provide additional, useful information. Pre-market studies are essential when a product's dosing information or safety and efficacy profiles are not well-defined. In those situations, such studies are necessary in order to ensure that prescribing physicians have enough information to use the drug appropriately. With generics--chemical drug or biologic--the post-marketing experience of the brand product, together with the demonstration of comparability provide this information, make extensive clinical testing programs unnecessary and duplicative. This has become apparent as FDA has determined that drug manufacturers can demonstrate that chemical generic drugs are safe and effective without repeating the full set of clinical testing required for the initial product. Congress should confirm that FDA has the authority to reduce testing requirements for generic biopharmaceutical products to only those necessary to ensure safety and efficacy. Generic biologics are being supplied by Sicom, LG Chemicals, GeneMedix, Cangene, Rhein Biotech, Dr. Reddy's Laboratories, Wochart

and Dragon Biotech and include human growth hormone, interferons, EPO, insulin and other biopharmaceutical products in markets such as Lithuania and other Eastern Europe markets, Mexico, China, Korea, India, Argentina, Egypt, Peru and Brazil. In any event, this information is really only additive to the experience obtained in the U.S. as companies submit applications. If they have marketed the product outside the U.S., they will have access to the safety experience and will be able to use this information to support the application. FDA may rely on this information as appropriate.

QUESTIONS SUBMITTED BY SENATOR CHARLES E. SCHUMER

1. Do you believe that it is now, or will be soon, possible to create a generic substitute for every biologic product that is produced? To what extent does the complexity of marketed products differ?

Response: There is a wide range in both the complexity of marketed drugs and biological products and in our ability to characterize them. While a substantial number of the products that exist today should be eligible for generic competition, there certainly are some that will not be appropriate for a generic approval for many years. This is why it is important to give FDA both the clear authority to approve generic biopharmaceutical products where we have sufficient scientific knowledge and the discretion to decide on the appropriate testing requirements on a product-by-product basis as the science dictates. Ultimately, we envision a system where FDA will be able to calibrate the regulatory requirements for a given product based upon the specific scientific issues it raises. Such an approach would ensure that there are not unnecessary regulatory burdens, but would also give FDA the authority to require more data where it is needed. It is important to note that there are still some drugs on the market that have no generic equivalent due to scientific challenges that have not, as yet, been overcome.

2. Scientifically speaking, how is it that companies are able to make follow-on products in other countries? Is the science any different from that which would be required to do the same in the US?

Response: For a significant number of biologic products, the science is sufficient to allow approval of generic counterparts based on reduced data requirements. The regulatory agencies in the countries that have permitted approval of generic biotech products apparently have determined that they have the legal authority to grant such approvals and that approval of these products is consistent with sound public policy. The U.S. FDA, on the other hand, has refused to decide whether it has the legal authority and apparently has decided to delay publishing even a draft guidance to advance productive discussion of this issue.

QUESTIONS SUBMITTED BY SENATOR DEWINE

1. In your testimony, you state that “biogenerics” are being developed, produced, and sold in Poland, China, and Lithuania. What approval standards were used to approve these “biogenerics” and how do they differ from the approval standards used in the United States? Do these countries currently comply with the TRIPS standards of the WTO for patent protection in developed countries? In what respects do the patent systems differ from the United States?

Response: We do not have information about the precise standards in Poland, China and Lithuania. But what is clear is that countries around the world are open to approving generic biopharmaceuticals. Even though there are several biologics for which generics could meet U.S. safety and efficacy standards (insulin and human growth hormone are two examples), the U.S. FDA has not been receptive to these products, which is why Congressional attention and action is so important. With regard specifically to patent protection, regardless of the actions of other countries, U.S. generic drug companies respect and uphold the patent rights of the branded companies and would continue to do so for biopharmaceutical products.

2. In the hearing you stated that the price of a follow-on biologic is estimated to be fifty percent less than for the innovator. What is your source for this statement? Are you aware of any other estimates in the public domain? If so, please provide them.

Response: In the United States today, generic drugs cost, on average, less than 30% of the price of brand products. Based on the experience with the non-biological generic drugs available in the U.S. today, we believe that it can be conservatively estimated that generic biopharmaceuticals will on average cost 50% of the cost of brands. This projected savings would result from the fact that generic companies can perform fewer clinical trials and that they do not need thousands of sales representatives to sell and promote their drug products. If Congress establishes a pathway for the approval of biopharmaceutical products that limits the need for extensive drug development programs and provides for comparability claims, the savings may be significantly greater.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 16 2004

The Honorable Orrin Hatch
Chairman
Committee on the Judiciary
United States Senate
Washington, D.C. 20510-6275

Dear Mr. Chairman:

Thank you for the letters of July 6, 2004, containing follow-up questions for the Food and Drug Administration (FDA or the Agency) from the June 23, 2004, hearing entitled, "The Law of Biologic Medicine." We have restated your questions below with our response for the record.

Questions from Senator Orrin G. Hatch

To Dr. Crawford

- 1. Please comment on trade secrets, and any other major factors that will be discussion points on how to regulate follow-on proteins, especially considering issues of safety and effectiveness of these products.**

The "major factors" that should be discussed in determining how to regulate follow-on proteins fall into two general categories: First, there are numerous scientific issues relating to how and to what degree one can assess the "sameness" of two proteins. We mention these scientific issues first, because they are the ones that relate most directly to assessing the safety and effectiveness of follow-on proteins. Second, there are legal and policy issues that need to be considered in a comprehensive discussion of follow-on proteins. Among these issues, and in no particular order, we believe it is necessary to be cognizant of: protecting trade secrets and confidential commercial information; making sure that nothing we do amounts to an unconstitutional taking of property without due process of law; assuring that patent rights are protected; maintaining incentives for industry to innovate, while appropriately balancing the need for lower cost follow-on products; and minimizing, to the extent compatible with assuring product safety and effectiveness, the regulatory burden.

- 2. You testified that under section 505(b)(2) of the FDCA, the agency may approve a new drug application (NDA) based, at least in part, on FDA's earlier finding that a drug is safe and effective. In doing so, is the agency using the data that supports the earlier approval to support the approval of the 505(b)(2)**

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application, or is the agency only relying on the final finding of safety and effectiveness for the earlier approval? Or is it both?

Under the 505(b)(2) approval mechanism, FDA may approve a new drug application (NDA) by relying on the finding of safety and effectiveness for the earlier approval.

- 3. Does the FDA consider there to be a distinction between reliance on a prior finding of safety and effectiveness and reliance on the underlying proprietary data that supported the finding of safety and effectiveness. Is there a legally significant difference?**

When FDA approves a 505(b)(2) application that relies on the Agency's previous finding of safety and effectiveness for a drug product, it does so to the same extent as is contemplated by the abbreviated new drug application (ANDA) approval process. That is, the applicant seeking approval for the new product must show that its proposed product is sufficiently similar to the approved product to be able to rely on the conclusions the Agency has made regarding the approved product's safety and effectiveness. The Agency's finding of safety and effectiveness is, of course, based on studies conducted by the sponsor. However, a subsequent ANDA or 505(b)(2) applicant does not rely on the study data directly, but rather on whatever findings FDA has already made about that data to support a drug approval. This is important because the data in an NDA may go well beyond what was needed to support the earlier approval. Therefore, FDA has determined that there is a legally significant distinction between reliance on a prior finding of safety and effectiveness and reliance on the underlying proprietary data that supported the finding of safety and effectiveness.

- 4. As you mentioned in your testimony, the agency is prohibited from disclosing trade secret and confidential information to the public. What guidance does FDA provide to its medical review staff with respect to the need to protect such information from disclosure? Is the review staff permitted to review, for example, manufacturing specifications in one sponsor's marketing application before providing comments on another applicant's manufacturing specifications?**

All staff, including medical review staff, are sensitized to their obligation to protect trade secret and confidential commercial information from inappropriate disclosure. All new employees are trained early in their employment on this obligation and are required to acknowledge it in writing. The Agency periodically reminds staff of the need to safeguard protected information.

For example, FDA's Center for Drug Evaluation and Research reviewers who work on NDAs, including applications covered by section 505(b)(2) of the Act, are apprised of policies relevant to their reviews. Reviewers are advised, for example, that they can rely on prior Agency findings of safety and effectiveness for approved drugs in reviewing generic drug applications. This reliance is, however, distinct from using specific data owned by one sponsor, which underlies a prior Agency finding, to fill a "gap" in another sponsor's application that needs to be filled in order for the application to be approved. We prohibit the latter type of reliance unless authorized by the relevant sponsor. Consistent with the above,

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reviewers can and do consult previously approved applications for background or other purposes not related to unauthorized "gap filling," including in scenarios such as the one you describe. (In fact, reviewers are sometimes unavoidably conscious of information in a prior application, even without physically consulting the application, simply because they recall the information from having worked on the earlier review.)

Questions from Senator Richard J. Durbin

To Dr. Crawford and Mr. Troy

The FDA has promised a guidance document for an approval process for "follow on biologics" by Fall, 2004. In addition to addressing the biological, medical and technical aspects of producing generic equivalents, will the document address the legal issues associated with (a.) the regulation of biologics under the Food, Drug and Cosmetic Act and the Public Health Service Act; (b.) how both of these laws might apply to "follow on biologics"; and (c.) recommendation for changes to each of these laws?

No. The draft guidance that FDA will prepare is not expected to address legal issues; it is intended to address the science of follow-on proteins.

Questions from Senator Charles E. Schumer

To Dr. Crawford

- 1. In March of this year Dr. Mark McClellan, then Commissioner of the FDA, said "we do believe the science may be adequate now to proceed on several relatively simple biologics that were approved as NDAs, and hence are subject to Hatch-Waxman laws." It was my understanding that the FDA planned to issue draft guidance this summer to clarify FDA's current thinking on this issue and to lay out the scientific parameters relevant to the creation of follow-on biologics. Now it seems this guidance is being delayed. I understand you plan to hold a public symposium first, but that it isn't expected to take place until the fall. FDA has tremendous scientific expertise here, and you have said you have the authority to approve follow-on versions of products regulated as drugs under section 505 of the Food, Drug & Cosmetic Act (FD& C Act). We may not be able to approach this with a one-size-fits-all solution. If the science and the regulatory pathway are both there for some products, what is the reason for the delay? Why not issue guidance *now*, based on FDA's own scientific knowledge base, and get the discussion going, so that we can at least begin to move forward on the products we do know something about?**

FDA shares your desire to accelerate the discussion on this topic, and it is precisely our commitment to fostering a meaningful public discussion that has driven our anticipated schedule. Since the June 23, 2004, Judiciary Committee hearing, we have further solidified

our plans. FDA will hold a two part workshop exploring science issues relating to follow-on proteins: the first will be a public meeting in early fall at which the Agency will solicit public input on the numerous scientific issues relating to follow-on proteins (regardless of their legal approval mechanism); the second part is a cosponsored workshop with the Drug Information Association that will solicit the views of experts in a public forum. Given the fast-changing state of the science and the precedent-setting nature of the questions presented, FDA desires to make the anticipated scientific guidance as accurate as possible, and we need the public discussion to make this happen. There may well be certain "relatively simple" proteins for which it is appropriate to proceed with some form of follow-on. However, because the issues raised by these relatively simple products also implicate more complex products, FDA believes it makes sense to proceed with the benefit of public and expert input.

2. **In 1996, and in an updated version issued in 2003, the FDA issued guidance which allowed brand companies who have made manufacturing changes to show their new product is "comparable" to the one that was originally approved. Don't these documents provide a good framework for how a generic company might be able to do the same? Doesn't the guidance show- at the very least- that it's scientifically possible to show "comparability"?**

The 1996 guidance document is entitled, "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products." This guidance document has not been updated. FDA has issued subsequent guidance concerning comparability protocols. FDA issued the 1996 guidance to address the situation in which a single manufacturer makes changes to its own manufacturing process and must demonstrate comparability between the "old" and the "new" products. For scientific and legal reasons FDA limited the guidance to a single manufacturer. This guidance document could, in theory, provide a starting point for developing a scientific framework to demonstrate comparability between two products from two different companies. The general concept of comparability may be applicable to follow-on biologics if a number of additional factors are taken into account, as outlined below:

- 1) To demonstrate comparability between a commercially available innovator product and a follow-on product, the follow-on manufacturer would need to determine whether or not the formulation of the innovator's product contains components that would interfere with a thorough analysis of the characteristics of that product's active ingredient. In such cases, the innovator's active ingredient would need to be purified away from the interfering substances, without altering the qualities of the active ingredient, prior to being subject to a thorough characterization.
- 2) Some biotechnology products are more complex than others; for the most complex, the details of how the manufacturing process is performed can have a significant (and, in some cases, unpredictable) impact on the product's characteristics. Therefore, initial forays into the world of follow-on biologics will be most successful for those who work with relatively simple proteins (e.g., highly purified proteins that are not complex mixtures of variants).

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- 3) The innovator company may have a very specific, proprietary assay method that it uses to evaluate the potency of its product. The follow-on manufacturer would need to develop its own assay method to compare its product to the innovator's. It would also need to ensure that the assay method used for this comparison and for routine product quality testing is relevant to the clinical activity of the product.

3. Did the FDA conduct a widespread public symposium prior to issuing the initial draft of the 1996 comparability guidance for brand companies?

The concept of biochemical comparability was publicly discussed at public forums such as scientific meetings and conferences prior to issuing the draft. FDA did not hold a public symposium prior to issuing the draft 1996 Comparability Guidance, to our knowledge.

4. FDA has stated publicly that certain biotechnology products, for example Human Growth Hormone, may be approved based on limited clinical studies. I can only assume that FDA's saying this indicates that the Agency believes this can be done with no ill-effect on the public health. Is that the case? Does the Agency still believe this, and if so, why has the Agency chosen to delay issuance of the scientific guidance which might flush out this position?

As you indicate, we continue to believe that applications for human growth hormone (hGH) can be approved based on less clinical data than would be required for other products whose clinical effects are not as well understood. We are delaying the issuance of a scientific guidance (which will be applicable to therapeutic proteins and peptides beyond just hGH) because additional time is needed to prepare the guidance. In substantial part, a delay is necessary because we are committed to ensuring that a full public discourse takes place before the guidance is completed. We believe that engaging in an open discussion before proceeding with the guidance is critical given the complexity of issues and controversy surrounding our work on this document. As you have noted, we are convening a public workshop this fall. We will solicit public input on key scientific issues during this workshop. The fall workshop will be followed by a second scientific workshop in early 2005. To help enhance the discussion at the second workshop, we will issue a concept paper in advance that is based on our consideration of the public input we receive during the fall session. We believe this multi-step public process will best ensure that our guidance is robust and addresses all pertinent issues.

- 5. Some have argued that it is not possible to determine that two biologics are "interchangeable". However, it is my understanding that the FDA already has some experience making such a determination. Specifically, the package insert for a hepatitis-B vaccine, Engerix-B, describes studies which indicate that Engerix-B, which is yeast-derived, is interchangeable with other manufacturers' plasma-derived vaccines. How did the FDA make the determination that these vaccines were in fact interchangeable? On what science did FDA base its approval of this statement? Did the Agency require the companies to do**

additional tests? What from this experience is transferable to the determination of interchangeability of follow-on biologics? Doesn't this action by the FDA clearly indicate that science exists to allow for similar determinations for other follow-on products?

It is true that the package insert for Engerix-B contains a subsection, in the Clinical Pharmacology section, concerning the vaccine's interchangeability with other hepatitis B vaccines. This subsection states that, based on *in vitro* and *in vivo* studies, "it should be possible to interchange the use of Engerix and plasma-derived vaccines (but see CONTRAINDICATIONS)." However, as described below, interchangeability in this vaccine context is largely based on antibody response, and is thus separate and distinct from any notion of demonstrating sameness between follow-on therapeutic protein products.

Serum antibodies against the surface protein of the hepatitis B virus (the hepatitis B surface antigen, abbreviated as "HBsAg") are a well-accepted correlate of human protection against hepatitis B disease; there is general agreement that 10 milli-International units/mL (mIU/mL) of such antibodies are protective. Currently, there are two hepatitis B vaccines in use in the United States, Recombivax HB from Merck and Engerix-B from Glaxo Smith Kline (GSK). Each is a recombinant DNA-produced version of the HbsAg; both recombinant vaccines are produced in yeast. Although similar, there are differences in the vaccines and vaccine formulations. For example, the Merck vaccine is formaldehyde-treated (thus modifying the HbsAg protein), whereas the GSK vaccine is not. The pediatric dose (for children born to mothers who are not positive to the HBsAg) of Recombivax HB, administered on a 0, 1, and 6 months schedule (i.e., the second and third doses are administered at one and six months, respectively, after the first dose), is 5 µg; the pediatric dose of Engerix-B, administered on the same schedule, is 10 µg.

Both vaccines are comparable in sero-conversion rates to the 10mIU/mL level – essentially 100 percent for healthy infants and in excess of 95 percent for healthy adolescents and young adults (< 40 years of age); there is an age-dependent waning of vaccine response that is observed with both vaccines. The antibody responses that are seen with the two vaccines are highly similar in nature (not just in level) in that no differences were seen between them and the previously licensed plasma-derived hepatitis B vaccine. Both vaccines demonstrated clinical efficacy, among other things, in preventing disease in neonates born to hepatitis B infected mothers.

Both recombinant vaccines demonstrated interchangeability with the then-licensed plasma derived vaccine (the plasma-derived vaccine is no longer manufactured, having been replaced by the recombinant DNA derived vaccines). This interchangeability was evidenced by the similar nature of the antibody responses to the respective vaccines (see P. Hauer *et al.*, *Postgrad. Med. J.*, 63 (Suppl 2), 83 – 91 (1987); cf., West, D.J.; Calandra, G.B.: Vaccine induced immunologic memory for hepatitis B surface antigen; implications for policy on booster vaccination, *Vaccine*, 14(11): 1019-1927, 1996. Emini, E.A.; Ellis, R.W.; Miller, W.J.; McAleer, W.J.; Scolnick, E.M. and Gerety, R.J.: Production and immunological analysis of recombinant hepatitis B vaccine, *J. of Infection*, 13(Sup. A): 3-9, 1986; Brown,

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S.E.; Stanley, C.; Howard, C.R.; Zuckerman, A.J.; Steward, M.W.: Antibody responses to recombinant and plasma derived hepatitis B vaccines, *Brit. Med. J.*, 292: 159-161, (1986). In an additional clinical study (L.M. Bush et al., Evaluation of initiating a hepatitis B vaccination schedule with one vaccine and completing it with another, *Vaccine*, 9, 807 – 809 (1991)), it was shown that Engerix-B could be used to complete a course of immunization begun with Recombivax HB (serological responses to two doses of Recombivax HB followed by one dose of Engerix-B were similar to three doses of Recombivax HB).

In summary, the licensure of each vaccine was separately based on (1) clinical studies of efficacy against a disease end-point and (2) very high rates of seroconversion in vaccine recipients to a well-established correlate of immunity (i.e. anti-hepatitis B surface antigen serum antibody levels in excess of 10 mIU/mL). The given interchangeabilities of the vaccines, which are limited (*vide infra*), were based on clinical studies in human vaccine recipients demonstrating that comparable antibody responses were achieved. The interchangeability that is allowed is limited to those instances that were studied clinically; for example, Engerix-B may not be used interchangeably with Recombivax HB for the accelerated adolescent schedule.

- 6. Is it the case that, in the interest of public health, the FDA has assigned certain therapeutic proteins to be reviewed under the NDA route in the FD&C Act as opposed to under the BLA route in the Public Health Service Act (PHSA)? Doesn't FDA have the ability to select the legal mechanism under which a product will be approved, when it is in the interest of the public health? Are there any limitations on this authority? If so, what are they?**

Whether a particular approval mechanism is "in the interest of public health" is not the standard that FDA uses in determining how a product will be regulated; rather, since our approval authority derives from statute that determination is made by reference to statutory language and definitions. If a product fits the definition of a biologic under section 351(i) of the Public Health Services Act, it is regulated using a biologic license application (BLA). If a product does not fit the definition in the Public Health Services Act, its intended use will nonetheless make it a drug, subject to regulation under an NDA (or in some cases, a device, subject to regulation under the device authorities). You are correct that because of the interpretation of the definition in the Public Health Services Act, there are a limited number of protein products regulated as drugs under section 505 of the FD&C Act. These include products such as insulin and human growth hormones.

- 7. I have heard from industry sources that for certain classes for which FDA has approved multiple similar biologics, the Agency has been able to refine the clinical requirements for applicants after the first. Is this the case?**

It is common to refine clinical requirements after some experience with products in a class. This phenomenon is not limited just to biologics. FDA frequently learns things from the first product applications in a class that can help refine study design issues for subsequent products, either in terms of safety or efficacy.

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For instance, pre and post approval (or licensure) experience with a product as well as increased knowledge about the disease or condition that a product is intended to treat, may aid in refining subsequent clinical studies with similar products. Such information might, for example, lead to the establishment of surrogates such as a correlate of protection that can subsequently be used as the basis for demonstrating efficacy for product licensure or approval. Similarly, information about safety problems encountered with members of a class may lead to the need for specific safety monitoring during clinical trials of new members of the class.

Question from Senator Joseph R. Biden, Jr.

To Dr. Crawford

- 1. Many biologics are quite complex and are used to treat very specialized segments of the population. These will not be so-called "blockbuster" products. Do you think that some biologics lend themselves more to "follow on" versions than others? How do you think we should deal with more complex biologics that may be more difficult to replicate? What about products that are akin to "orphan drugs" only aimed at a limited group of patients?**

Proteins vary in complexity. Many highly sophisticated analytical methods have been developed permitting more accurate characterization of complex proteins, and as science improves, more advances can be expected. In general, some proteins clearly lend themselves more to "follow-on" versions than others. Larger, more complex (e.g., with varying degrees of post-translational modifications or consisting of multiple sub-units) are more difficult to evaluate and handle than smaller, less complex molecules

While market demand is likely to drive development of follow-on products, limited use products may only have one manufacturer. Orphan designation is available for products regulated under a BLA.

Thank you again for contacting us concerning this matter. FDA appreciated the opportunity to testify before the Subcommittee. Please let us know if there are further questions.

Sincerely,



Patrick Ronan
Assistant Commissioner
for Legislation

DR. HANCOCK
RESPONSES TO QUESTIONS FROM THE COMMITTEE
THE LAW OF BIOLOGIC MEDICINE
JUNE 23, 2004

Questions from Senator Hatch:

1: *What is your position on the development of generic biologics? Do you believe it is possible with all biologic products? If not, when is it possible to develop such products?*

My position is that there is not yet sufficient science necessary for the development of safe generic biologics. I feel especially strongly about this point if the way of prescribing such products would be like the current system for small molecule drugs where generic drugs can be interchangeable with brand name drugs. For it to be possible to develop such generic products, there would need to be significant advances in both methods of characterization and methods of regulating production of biotechnology products.

2: *In your testimony, you talk about substantial scientific challenges to achieve the adequate characterization of any biotechnology product. Could you please go into more detail for us? What do you believe are those substantial scientific challenges? Is it possible for us to overcome such challenges?*

It is important that this question uses the term "adequate characterization." Current scientific methods permit a level of characterization sufficient for a manufacturer to develop a biologic product and test it for safety and effectiveness. However, this characterization is highly specific to the particulars of the manufacturing process. Current science is not advanced enough for a 'full' characterization in an absolute sense, such as is possible with a small molecule drug.

The main scientific challenges stem from the facts that one is dealing with biological systems and that the products can be heterogeneous. The process for creating biotechnology products involves growing the protein in a biological system, whether it be a mammalian system, like a hamster ovary cell line, or a bacterial cell like *E. coli*. The fermentation process for growing colonies of cells to produce biologics is much less exact than the typical chemical synthetic processes used to produce small molecule drugs and therefore not completely reproducible. This means that one needs to apply systems biology approaches to completely characterize the manufacturing process and the product. Systems biology is in its infancy and a long way from being able to fully characterize these processes.

The other significant scientific challenge is the heterogeneity typically found in biotechnology products. Unlike a small molecule drug like aspirin, a biotechnology

product may not be a single molecular species. Rather, a batch of the product may contain a mixture of molecules that vary in important ways even though they have the same basic structure. Even if a batch of a particular protein biologic was characterized and shown to have a consistent amino acid sequence, there are over 200 known modifications (called post translational modifications) that can supplement and change the protein structure without affecting the amino acid sequence. One common example of this variability is glycosylation, or addition of sugar (carbohydrate) residues. A protein biologic might have a consistent amino acid backbone, but have inconsistent changes in the carbohydrate branch structures which could affect the biologic's potency and safety. There are presently limits to how well one can test for this heterogeneity. On the other hand, once a company has produced a product and tested it for safety and effectiveness, including human studies, it can control the manufacturing process to the point where the degree of heterogeneity is consistent within product specifications.

Another significant point is that proteins tend to aggregate, forming clumps of various sizes, which leads to a non-uniform formulation. Differences in aggregation can affect the safety and effectiveness of a biotechnology product. For instance, if proteins form large enough clumps they can precipitate, or come out of solution, rendering them completely inactive. This is not an issue for a small molecule drug like aspirin, because content uniformity can be standardized and tested for such a drug. For proteins, however, there are limits to the utility of standard tools like chromatography as a means to test the differences in aggregation.

As for overcoming the scientific challenges, I believe that it is possible to improve characterization methods somewhat. Science is also continuing to uncover information about how cells grow and produce proteins, and this will be helpful for understanding the systems which produce biologics. We should also advance the state of knowledge by sequencing the genome of the Chinese hamster, a species commonly used in biotechnology manufacturing processes. Whether one can overcome the challenges in characterization may depend on what level of comfort people want with respect to the detailed characterization of products. Given how much the identity of a product is dependent on the manufacturing process used, however, it would be perhaps more important to develop and require better process tests and controls. These tests and controls would also be of particular importance for the raw materials, especially those from overseas. Raw materials used to feed the cells that make biologics come from animal sources, and in addition to the process variability due to unspecified impurities, one must be constantly vigilant against viral contamination.

3: You talked about the substantial differences between small or simple molecules drugs and biologics. For those of us who do not have scientific backgrounds, could you explain whether or not it is possible to create a generic biologic from a small molecule biologic? Is it possible to develop a generic biologic from a large molecule biologic?

I do not use the terms small and large molecule biologics. However, there is certainly a spectrum of molecular weights for biologics ranging from the smallest proteins, like insulin, to molecules that are many times larger. Therefore, I understand the question as basically asking whether there are differences in the possibility of creating generic biologics depending on the size of the molecule.

Although the relative size of a biologic's molecule certainly would affect the ease in which certain characterization processes can be performed, it does not affect my view on whether one can create a generic biologic. Rather, the key fact is that, regardless of the size of the biologic, it is the manufacturing process which creates much of the complexity associated with biologics. Any changes in that process need to be carefully evaluated. For example, safety problems were encountered when some people switched from animal insulin to human biotechnology products.

Question from Senator Durbin

1.) *Mr. Schultz mentioned in his statement that the FDA needs to have flexibility to calibrate any regulatory requirements to fit the particular circumstances of each individual biologic since the complexity of biologics "vary along a continuum."*

a.) *Would a case-by-case regulatory protocol be the best way to assess the safety, efficacy and therapeutic equivalence of follow on biologics?*

b.) *Would a case-by-case regulatory scheme create unnecessary complexity in the approval process?*

I think that good science is the proper test. As I mentioned in my testimony, I do not believe that current science is adequate to consider follow-on biologics, especially biotechnology-derived protein products. Given how much of a biotechnology product's distinctiveness and consistency is tied to the manufacturing process, it is hard for me to see how such products can be categorized for purposes of consideration.

However, if Congress were to determine that there could be follow-on versions of at least some biologic products, then one could consider setting up a regulatory scheme that would assess which products would be eligible and what standards would be applied. The problem is where you would draw a line. When I think about how one could view the continuum, I still come back to the idea that the line may be whether the product is prepared using biological methods. On the other hand, biologics vary in complexity, and each biologic produced by each manufacturer is unique. Unless a very conservative approach were taken and the standards were targeted at the most complex product, applying the same standards to the simplest biotechnology product as to the most

complex one would seem to create safety risks not worth taking. Thus, in a world where follow-on versions could be approved for at least some biologics, a case-by-case regulatory protocol may be the best way to assess the safety, efficacy and therapeutic equivalence of the products, regardless how complex this may make the process. I also think it would be important, once the science is far enough advanced for a law to be written, for Congress to make sure that FDA follows an orderly process for each individual biologic to get full scientific input before it establishes the specific requirements for follow-on versions of that product.

Response of William B. Schultz, on behalf of GPhA, to Questions Submitted as Follow-up Senate Judiciary Committee Hearing, "The Law of Biologic Medicine" (June 23, 2004)

QUESTION SUBMITTED BY SENATOR HATCH

One of the areas of disagreement in the area of biopharmaceuticals is in the proper terminology for their generic products. The brand name companies abhor generic biologicals, and suggest follow-on biologicals, in your testimony you state that the generic industry prefers "generic biopharmaceuticals." The Europeans propose using off-patent biotechnological products (OPBP) for describing such products. Would that be an acceptable terminology?

Response: As we noted in our testimony at the hearing, we have chosen to use the term "generic biopharmaceuticals" while we are in the process of determining the most appropriate nomenclature for these products. While we are evaluating different terminology that could be used, one term that we believe is inappropriate is the term "follow-on biologics," largely because it suggests that those products are secondary or somehow inferior to the products already on the market. In addition, the term "follow-on biologics" is imprecise, since it apparently would cover both brand products that may be marketed after the original brand product as well as generic products. In its April 8, 2004, citizen petition to FDA, the brand company Genentech raised similar concerns that the term "follow-on biologic" had been used for products that came on the market based upon a full complement of data after a pioneer product had been approved.

As we continue discussions over the proper nomenclature for these products, we recognize that the precise terminology for a product does affect how it is perceived. In our analysis, we certainly will evaluate the European term "off-patent biotechnological product" and other suggested terms. We expect that we will be back in contact with both FDA and your office in the near future with our recommendation for the proper nomenclature for these products.

QUESTION SUBMITTED BY SENATOR PATRICK LEAHY

I understand that the National Organization for Rare Disorders is particularly interested in a fast-track system for approving generic biotech medicines that treat rare disorders, while others have recommended a slower approach to ensure the safety of the products. What course do you recommend for the FDA in order to properly balance these interests? Do you believe Congressional action is needed before guidelines are issued by the FDA?

Response: The paramount consideration with regard to generic biopharmaceuticals is that these products meet FDA's high standards for approval and the product is safe and effective for its intended use. GPhA strongly endorses the agency's current safety and efficacy standards. The agency's scientists grapple with novel issues daily in evaluating applications for products to which the public has never been exposed. Since they involve versions of products that are already on the market, the issues raised by generic biopharmaceuticals will be in the context of a known product, and in many cases the safety and efficacy issues raised will be less novel than the issues that agency scientists must decide with respect to brand products containing a new

chemical entity. Americans should maintain its confidence in FDA to approve only those products that are safe and effective for their intended use, regardless of whether the product is a brand or a generic. Because the potential savings to consumers and healthcare providers are so enormous, the agency should adopt a process for expeditiously reviewing and approving generic biopharmaceuticals. Certainly the timeframe should be within the 6-10 month timeframe currently used for brand products.

We do not believe that Congressional action is necessary for FDA to issue guidelines. Instead, we believe that Congress should encourage FDA to issue regulatory guidance as quickly as possible. While FDA is proceeding on a track to provide the industry with the scientific guidance and even to issue approvals, Congress should clarify the agency's legal authority to avoid protracted litigation downstream.

QUESTION SUBMITTED BY SENATOR RICHARD J. DURBIN

You take the position that FDA has the authority now to adopt a new regulatory process for generic biopharmaceuticals. If that is the case, why is action by Congress in this area necessary?

Response: GPhA believes that FDA currently possesses the regulatory authority to approve generic biopharmaceuticals. However, as you know, FDA currently is wrestling with the scope of its authority in this area, and the agency has been unwilling to take definitive action by declaring its legal authority and issuing guidelines identifying scientific requirements. Moreover, even if FDA announces that it does have legal authority to reduce data requirements for generic biopharmaceuticals, the brand industry is likely to attempt to delay any approvals by initiating litigation. GPhA therefore believes that the most efficient course that would speed the availability of generic biopharmaceuticals to consumers is for Congress to pass legislation that specifically delineates FDA's legal authority in this area. Without such legislation, the issue of whether FDA has legal authority could languish at the agency level, and consumers could be denied indefinitely access to life-threatening and chronic medicines.

QUESTIONS SUBMITTED BY SENATOR CHARLES E. SCHUMER

1. The brand name industry argues that before any regulatory system for the approval of generic biopharmaceuticals is in place, the science needs to have evolved to the point where FDA can better evaluate whether a particular biopharmaceutical product can have a generic counterpart. You obviously disagree. Why?

Response: FDA is a science-based regulatory agency that is charged with making regulatory decisions based upon emerging science every day. FDA scientists and reviewers have demonstrated the capability to review cutting-edge science involved with new molecular entities. These products frequently raise new issues as to appropriate testing requirements to ensure safety and efficacy. The industry's assertion therefore that the science must be further developed before FDA can tackle these regulatory issues flies in the face of what we know about the agency and how it fulfills its mission of protecting and promoting the public health. By providing a basic legal and regulatory framework that is flexible enough to accommodate this dynamic industry, scientific innovation will be fostered and cost-effective products will be made available

to patients more quickly. Conversely, delaying action will stifle investment and innovation in this important area.

2. It is my understanding that the Drug Price Competition and Patent Term Restoration Act of 1984, the Hatch-Waxman Act, was based on a trade off — generic companies were granted an abbreviated approval process and the brand companies were granted patent restoration for time lost during the regulatory approval process. Do the patent restoration provisions apply to biological products as well, and if so, to all biologic products?

Response: It is our understanding that the patent restoration provisions under the Hatch-Waxman Act apply to biologic products. Specifically, under section 156(f) of Title 35, patent extensions may be granted to human drug products, which are defined as “the active ingredient of a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act) . . .”. Thus, this language explicitly covers drugs approved under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355, and biologics approved under section 351 of the Public Health Service Act, 42 U.S.C. §262. In addition, as the U.S. Supreme Court recognized in *Eli Lilly and Co. v. Medtronic, Inc.*, 110 S.Ct. 2863 (1990), when Congress adopted section 156(f) it adopted section 271(e) to overrule the Federal Circuit’s decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (1984). Section 271(e)(1), which applies to all human drugs, whether chemical or biological, states that “[i]t shall not be an act of infringement to make, use, or sell a patented invention . . . solely for uses reasonably related to the development and submission of information under Federal law which regulates the manufacture, use, or sale of drugs.”

3. What steps can the FDA and/or Congress take now to provide incentives to pharmaceutical companies to take the required risks to research and develop follow-on biologic products and file applications with the FDA as quickly as possible? How are these incentives relevant to the advancement of the science in this area?

Response: The most significant step that FDA and Congress can take to provide incentives to pharmaceutical companies to invest in the development of generic biopharmaceuticals is to clarify FDA’s legal authority and the requirements for obtaining approval of these products. In addition, Congress could earmark a certain portion the research funding already available to FDA’s Center for Drug Evaluation and Research for specific research in the area of emerging generic biopharmaceutical products. The agency spends tens of millions of dollars every year on research and it certainly would be appropriate to direct the agency to spend a portion of those funds to facilitate consumer access to affordable biopharmaceuticals.

SUBMISSIONS FOR THE RECORD



STATEMENT OF DAVID BEIER
SENIOR VICE PRESIDENT, GLOBAL
GOVERNMENT AFFAIRS

BEFORE THE
COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

JUNE 23, 2004

I. INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am David Beier, Senior Vice President for Global Government Affairs for Amgen Inc. I am pleased to be with you today to discuss the challenge of establishing an approval framework for follow-on biotechnology products. Amgen is the world's largest biotechnology company and is headquartered in Thousand Oaks, California, with locations in South San Francisco, Washington state, Colorado, Massachusetts, Rhode Island, Puerto Rico, Australia, Japan, and throughout Europe. Amgen has seven marketed products in the United States, including two of the most recognized biotechnology products, Epogen® (epoetin alfa) and Neupogen® (filgrastim). Last year, we invested 1.7 billion dollars in research and development on new therapies.

Amgen is a pioneer in the development of biotechnology-derived proteins, with experience covering the fields of molecular and cellular biology, target discovery, safety assessment, therapeutic delivery, and biotechnology process development. Few organizations in the world can claim to have Amgen's technical experience, and few have been able to deliver safe and effective biotechnology products to patients for so long with so few adverse events. Amgen's innovations have helped millions of people worldwide who have medical conditions for which there are few effective treatments. Our biological products help fight these diseases and improve the quality of people's lives. It is from this perspective that I comment

on behalf of Amgen on the issue of what some call “generic” and others, like the Food and Drug Administration (FDA), call “follow-on” biologics.

My testimony today will focus on the public policy and legal principles that are central to the debate on this issue. In particular, I will discuss five points:

- The ways in which biotechnology products are different from chemically-derived drugs;
- The landmark Hatch-Waxman amendments that created the generic drug approval process, and why it is not applicable to biotechnology products;
- The potential risks to patient safety posed by follow-on biologics;
- The need to protect and promote innovation in the biotechnology industry; and
- The need for a structured public process to explore the science of follow-on biotechnology products.

Before I address these points, I think it is important to frame what I believe are the defining principles in this discussion.

Amgen believes that patients and physicians deserve the best and safest medicines that technology can deliver. And, we believe that patients deserve access to the most cost-effective, competitively-priced therapies available. As we

have learned from the landmark system for the approval of small-molecule, traditional drug products, these twin goals are not mutually exclusive. They do, however, require exquisite balancing. For innovation to thrive, the needs and rights of pioneer manufacturers must be preserved, and the system as a whole must – without compromise or fail – ensure that patient safety is protected.

Thus, in developing any process for expanding the availability of biotechnology products, we believe there are three principles that trump all others:

- Always put patient safety first;
- Ground the process in sound science; and
- Fully respect innovator rights.

We believe that if these fundamental principles are maintained, through a sound public process, Congress, FDA, patients, and industry can develop a sensible roadmap for the approval of safe and effective follow-on biologics.

II. BIOTECHNOLOGY PRODUCTS

Biotechnology holds the promise of treating or curing the most devastating human illnesses, many of which remain almost completely untreatable today. In fact, almost half of the new products approved by FDA last year were biological products, and nearly 300 biotechnology products – for over 150 diseases, including cancer, Alzheimer's disease, heart disease, chronic kidney disease,

diabetes, multiple sclerosis, AIDS and arthritis – are currently in Phase III clinical trials.ⁱ To the 325 million patients who have been helped by these products, and to those waiting and hoping for a treatment or cure, biotechnology represents a beacon of hope in a dark night.

To understand the promise of these therapies, and to foster their continued development, we first need to understand what they are and how they are different from traditional drugs. Thus, I will briefly review – from the lay perspective only – the nature of biological products and, in particular, biotechnology products.

To begin, biological products are significantly greater than traditional drugs in size, structure, and complexity. Because they consist of large molecules, most biological products must be administered intravenously or by injection, usually in a doctor's office or hospital setting.

Biological products and, in particular, therapeutic proteins, are manufactured from living cells. This is an elaborate process, spanning several months and involving numerous steps. The process generally begins with the “programming” of a unique cell line (by genetic engineering or recombinant technology) to produce a certain protein. These cells may be derived from bacteria (like *E. coli*) or mammals (like Chinese Hamster Ovary cells). The use of cells in production requires highly controlled manufacturing environments, and the process

must be kept sterile and free of pathogenic microorganisms to ensure proper growth and safety of the desired protein.

The end product of this biotechnology manufacturing process is, most often, a complex mixture of heterogeneous proteins and impurities. Each of the closely-related proteins in this mixture contributes to the biological activity, efficacy, and safety of the product. The mixture in any one biological product is defined largely by its manufacturing process. This is because living cells are, in essence, the factory. While the cell can be programmed to produce a very specific protein, the cell is still a living organism; it cannot be controlled in the same manner that pharmaceutical engineers can control the synthesis of small-molecule drugs.

The protein molecule itself is a three-dimensional structure, often in the form of a long amino acid backbone with strands of carbohydrates appended in all directions. This structure can be described using an array of tests, but they can only describe specific parts of the protein structure. We have tools such as amino acid sequencing and peptide mapping, which provide some information about the product's structure. We can gain additional information on the identity, structure, heterogeneity, and biological activity of the product using additional tests such as chromatography, immunoassays and biomimetic tests.

However, the picture that can be drawn of a biotechnology product based on these types of measures is, unquestionably, incomplete. Animal studies and pharmacokinetic (PK) data can add to the picture, but it is not a picture from

which a complete determination of safety or effectiveness can be made. Most important, and in contrast to experience with small-molecule drugs, it is Amgen's experience that physico-chemical testing cannot establish "sameness" with regard to either the identity or the composition of one manufacturer's biologic to that of another. In other words, the chemical characterization of active ingredients in these products is inadequate to ensure sameness of efficacy (*i.e.*, "biological activity") and sameness of safety (*i.e.*, no unexpected adverse reactions, including immunogenic responses).

With these concepts in mind, it will be evident why – under current law – most biotechnology products are subject to a different approval process than small-molecule drugs and are not amenable to a true "generic" drug approval process.

III. LEGAL BACKGROUND

A. Hatch-Waxman

In 1984, Congress – under the leadership of the Chair of this Committee – amended the Food, Drug, and Cosmetic Act (FDCA) and U.S. patent law to establish an abbreviated application process for drug products that are in the twilight years of their patent protection. These amendments – titled the Drug Price Competition and Patent Term Restoration Act of 1984, but affectionately known as Hatch-Waxman – authorized FDA to approve generic copies of innovator drugs *without requiring an independent showing of safety and effectiveness*. Instead, the new law allowed generic companies to rely in full on data developed by pioneer

manufacturers, provided the generic could show chemical “sameness” to the pioneer’s product.

Prior to Hatch-Waxman, and with some exceptions, a pioneer company’s clinical data were considered to be proprietary in perpetuity. With Hatch-Waxman, the pioneer industry relinquished certain of its data protection rights to generic manufacturers in return for patent term restoration, various forms of data exclusivity, and a structured process for litigating patent disputes.

More specifically, under section 505(j) of the FDCA, a generic drug is considered to be the same as the pioneer – and is considered to be as safe and effective as the pioneer – if the generic has the same: (1) active ingredient, (2) dosage form, (3) route of administration, and (4) strength as the pioneer, and if the generic is shown to be *bioequivalent* to the pioneer. A bioequivalence study typically involves no more than two to three dozen healthy subjects, who often receive only one dose of the proposed generic and one dose of the pioneer drug.ⁱⁱ

With this showing of “sameness,” the safety and effectiveness of the generic product can be assumed. And, in fact, for small-molecule drugs, the science supports this assumption. Physical and chemical comparisons of small-molecule drugs are sufficient to assure that one manufacturer’s version will provide the same clinical benefit, and same risk profile, as another manufacturer’s version.

For this reason, FDA considers generic drugs to be interchangeable with the pioneer, allowing substitution with the full expectation that the generic

has the same clinical effect and safety profile as the listed drug. The agency assigns an “A” level therapeutic equivalence (TE) rating to such products and publishes these ratings in the *Orange Book*. Most state and federal health care systems rely on FDA’s TE ratings when substituting lower cost generics for brand name prescription drugs.

Finally, a handful of recombinant DNA products (*e.g.*, human growth hormone (hGH) and insulin) are, for historical and administrative reasons regulated solely as drugs. Nonetheless, follow-on versions of these complex protein products have not been approved under section 505(j) because it is not possible to determine that the active ingredient in one manufacturer’s version is the same as in another. In other words, the chemical characterization of active ingredients in these products is inadequate to ensure sameness of efficacy (*i.e.*, “biological activity”) and sameness of safety (*i.e.*, no unexpected adverse reactions, including immune response reactions). The agency’s experience with naturally-derived complex drugs such as Premarin® (conjugated estrogens) illustrates the difficulty of showing sameness for products where the specific active ingredients are not well-characterized.

Again, Hatch-Waxman is based on “chemical” sameness – the idea that one manufacturer can make an exact chemical copy of another manufacturer’s active ingredient. With complex substances, including certain products that are

regulated as drugs, we simply do not have the assurances we need to establish the safety and effectiveness of a proposed “generic” product.

B. The Public Health Service Act

For many of the reasons already discussed, biological products are subject to a separate premarket approval system from traditional drug products. Most biotechnology products are “analogous to” or derivative of live cellular products and, as such, meet the definition of a “biological product” under the Public Health Service Act (PHSA). They often target a specific aspect of the body’s immune system, and most biotechnology products themselves are large enough to trigger an immune system response.

For example, Amgen’s leading biotechnology products, including Epogen® (epoetin alfa), Neupogen® (filgrastim), Aranesp® (darbepoetin alfa), Neulasta® (pegfilgrastim), and Enbrel® (etanercept), are produced from gene-altered cells to form complex proteins. Like the body’s own erythropoietin, Epogen® stimulates the production of red blood cells in the body by triggering the division and differentiation of erythroid progenitors in the bone marrow. Neupogen® is a recombinant DNA version of a human protein that stimulates the growth of white blood cells, and Enbrel® targets tumor necrosis factor to reduce inflammation in patients with severe and debilitating rheumatoid arthritis.

Amgen is required to maintain a license under the PHSA for each of these products, and for each license, Amgen is required to meet the manufacturing

and labeling requirements applicable to all therapeutic products under the FDCA. To obtain a license under section 351 of the PHSA, sponsors must submit a biologics license application (BLA) and demonstrate that: (1) the biological product is “safe, pure, and potent;” and (2) “the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.”

The emphasis in the PHSA licensing standard on the manufacturing process and the “facility” is not to be overlooked; it reflects the long-held view that the manufacturing process has a significant potential to affect the quality of biological products, and the limitations in the ability to unambiguously characterize these molecules using current testing methodologies. While the Secretary of Health and Human Services is authorized to establish, by regulation, all requirements “for the approval, suspension, and revocation of biologics licenses,” the Secretary has never authorized the approval of biological products under an abbreviated application process. Rather, it is FDA’s longstanding position that original, product-specific, clinical data are required for each approval of a biological product. Much of the data innovators submit constitutes trade secrets or confidential commercial information.

IV. HATCH-WAXMAN DOES NOT PROVIDE A MODEL FOR THE APPROVAL OF BIOLOGICAL PRODUCTS

For small-molecule drugs, where sameness generally can be established to a chemical certainty, Hatch-Waxman represents a valid approach from a scientific perspective. It is quite another matter for biologics.

As I noted at the outset, on a relative basis, biotechnology products are significantly greater in *size*, *structure*, and *complexity* than small-molecule drugs. Biotechnology products are difficult to characterize with precision and impossible to characterize with certainty. They are made in cultures from living organisms, rather than synthesized from purified materials. These products (as well as the cells used to produce them) can react to imperceptible changes in temperature and light; and they can be affected by new processes, new solvents, and new methods of fermentation and purification.

A would-be sponsor of a follow-on biologic would be using a different cell line and different media to produce the protein, and would likely use different fermentation methods, purification processes, and specifications. Because of the inherent differences in these materials and processes, a generic sponsor cannot produce the same product as the pioneer. For example, even if the would-be generic sponsor and the pioneer both used Chinese Hamster Ovary cells to produce the biologic, each manufacturer's cell line would have its own sensitivity to the fermentation process. Each manufacturer would use its own *proprietary* cell culture or media to "feed" the cells, and each manufacturer would "feed" the cells at a different rate for a different period of time.

All of these factors bear on the composition, quality, and structure of the finished product. Given that the process depends on cellular metabolism, and that metabolism is sensitive to environmental factors, it is impossible for two manufacturers to produce identical protein products. In addition, it is impossible to determine – with only analytical and bioequivalence testing – that a follow-on biological product will be just as safe and effective as the pioneer product.

Thus, it is FDA's current position that an abbreviated generic approval process for follow-on biologics (akin to the Hatch-Waxman pathway for generic drugs) is simply not appropriate. Amgen agrees with this position. We believe that, as the science evolves and reaches a consensus, there may be opportunities to abbreviate certain of the requirements (likely *not* with respect to safety or manufacturing-related data) for follow-on products. Even then, we believe that legislation is required before FDA could formally adopt any sort of abbreviated approval process for any biologic. In the meantime, the scientific issues distinguishing biologics from small-molecule drugs, and the challenges of showing the "sameness" of biologically-derived products, must be explored.

V. PATIENT SAFETY

Biologics are some of the newest, most effective treatments for battling serious diseases. At the same time, biotechnology products interact with the body in new and unique ways. They often operate within the body's immune system and, unlike small-molecule drugs, they are large enough to be recognized by the body's

immune system. Taken together, this means that biotechnology products raise a qualitatively different set of risks than most small-molecule drugs.

For example, the antibodies that may be formed against a therapeutic protein can trigger serious clinical effects, including loss of efficacy and neutralization of the body's own essential biological functions. Many biotechnology products are designed to replace a deficiency in the body's own native or "endogenous" proteins. An immune response to such a product may result not only in the body neutralizing the therapy, but also in neutralizing its own native supply of the protein. While such events are very rare, they are rare because of the elaborate controls and extensive safety database systems that have been established to support all of the approved biologic products today.

The incidence of Pure Red Cell Aplasia (PRCA) in patients taking Eprex® (Epoetin alfa), an erythropoietin product, illustrates one such rare event. Erythropoietin is produced in the kidney and stimulates the production of red blood cells in the body. Eprex® is a recombinant DNA version of erythropoietin manufactured by a subsidiary of Johnson & Johnson for use outside of the United States. Based on a longstanding agreement between Amgen and Johnson & Johnson, Eprex® is made using the same basic technology that is used to make Amgen's own Epoetin alfa, known as Epogen®. However, in the late 1990s, it was reported that Johnson & Johnson made several changes to the manufacturing

process for Eprex®. Those changes have been linked in time to an increase in immune reactions in Europe to Eprex®.

Since 1998, more than 160 Eprex® patients have developed neutralizing antibodies to the product and to their own naturally occurring erythropoietin.ⁱⁱⁱ These patients were unable to stimulate the production of new red blood cells, even after Epoetin alfa treatment was discontinued. Some of these patients were required to take immunosuppressive drugs, and others required blood transfusions or kidney transplants. Many of these patients could be dependent on blood transfusions for the rest of their lives. To date, no reports of antibody-mediated PRCA have been reported in relation to Amgen's version of the product, Epogen®.

This type of immunogenicity is one example of the potential for significant safety concerns related to follow-on biologics. It illustrates how a manufacturing change may – and I emphasize may, because the cause of these incidents is still under investigation – result in unpredictable and potentially irreversible adverse reactions.

Such reactions may be a function of glycosylation and the unique folding of the protein structure, each of which is specific to the particular manufacturing process. Minor species and impurities, which are also present in biological products and are specific to the manufacturing process, can also contribute to immunogenicity. Unfortunately, neither analytical testing nor testing

in animals can predict whether, or at what rate, a biological product may trigger a serious immune response in humans. It is also unlikely, if not impossible, that two biological products produced by different manufacturers would have the same immunogenicity profile.

In short, biotechnology products present numerous challenges from a patient safety perspective. Before we begin to expand the market for such products, through the introduction of follow-on products, we need to fully understand the nature of these risks and evaluate the science that would be needed to assure that these risks can be managed across a wider array of manufacturers. It is imperative that these safety issues are addressed by Congress and resolved by the relevant medical experts before we can responsibly support a system for the approval of follow-on biological products.

VI. INNOVATION: PROTECTING AND STIMULATING ADVANCES IN RESEARCH AND DEVELOPMENT

In 1984, when the Hatch-Waxman amendments were passed, there were tens of thousands of marketed drug products, many of which had been safely used for dozens of years. FDA, the medical community, and the public had decades of experience with these products. By contrast, today there are only about 155 approved biotechnology products, most of which were approved very recently.^{iv} While the entire biotechnology industry doubled in size between 1993 and 1999,^v biotechnology is still very much in its infancy compared to the state of the larger drug industry when Hatch-Waxman was first being debated.

In looking ahead at expanding access to biotechnology products, we must be sure to retain the incentives for pioneers and investors to take the enormous risks that are needed to sustain innovation in the industry. Put differently, in creating new policy, we must maintain an incentive structure that stimulates the level of innovation that has driven the United States to be the leader in research and development up to this point.

For example, the development of just one pharmaceutical drug costs an innovator at least \$800 million on average^{vi} – and the cost of developing a biological product could be even more. Moreover, in 2002, research and development spending by the United States pharmaceutical industry was approximately \$28 billion – almost 41% more than R&D spending in Europe.^{vii} In the same year, the U.S. biotechnology industry spent \$20.5 billion on research and development.^{viii} These figures are just one indication of the United States' position as the world leader in terms of research and development, innovation, and job creation in the pharmaceutical and biotechnology industries.

Thus, a critical issue in creating any sort of follow-on biologics approval process must be: How can the law encourage innovation *and* competition? How can Congress assure access to biological therapies while preserving patent protections and other market incentives for the development of new therapies? Without keeping one eye on the innovation side of the issue, patients ultimately will

lose if there is no longer sufficient incentive for companies to engage in the expensive and risky new drug development process.

This is especially critical in the area of biotechnology, where success represents the exception rather than the rule, and where 40 to 50% of candidates fail in Phase III studies.^{ix} The vast majority of biotechnology companies are not profitable today, and are highly dependent on the flow of venture and investment capital to complete the research needed to bring their first product to the marketplace. To remove or undermine incentives for new research and development at this time, while we are on the cusp of so many exciting biotechnology breakthroughs for so many diseases, would be a terrible blow to innovation and the public health.

The good news is that we know Congress can have a profound impact on the stimulation of innovation. The Orphan Drug Act of 1983 may be the best example of this. Before the Act, there were less than ten approved orphan drugs.^x Today, there are nearly 250.^{xi} These new orphan treatments are helping more than 12 million patients in the United States.^{xii} The Act achieved this by offering a seven-year period of market exclusivity after approval, as well as government grants, tax credits, and other incentives, for any new orphan drug.^{xiii}

This type of legislation illustrates the clear cause-and-effect connection between economic incentives and innovation. Just as congressionally-created incentives were critical to attracting companies to invest in orphan drugs and

pediatric studies, so, too, will such incentives be critical to keep biotechnology companies investing in new, ground-breaking biologics research and development.

VII. INNOVATION: PROTECTING INNOVATOR TRADE SECRETS AND PROPRIETARY DATA

Strong intellectual property and data protection laws are a cornerstone of any innovation-driven industry. Innovators must be able to rely on the protection provided by patents and trade secret law. When a biotechnology innovator submits a BLA, it provides FDA with extensive trade secret and other confidential data, encompassing years of research and clinical studies. This information is provided specifically for the approval of the innovator's biologic and should be regarded as proprietary and strictly confidential unless the innovator consents to its public release or as required by law. Current law governing biologics does not give FDA the authority to infringe on these innovator rights.

Thus, as FDA recently noted, the data required for the approval of any new product (even a follow-on product) "must be in the public domain. FDA does not have the legal authority to reference information in an innovator company's BLA submission."^{xiv} This principle is also reflected in FDA's regulations, which memorialize the agency's longstanding position that summaries do not constitute full reports of investigations. Even if summaries of clinical studies are available in medical journals, for example, these are clearly not sufficient to establish substantial evidence of safety and efficacy. Only Congress can change this

paradigm to strike a balance between protecting innovator rights and establishing guidelines for follow-on biologic approval.

Finally, the Fifth Amendment of the Constitution prohibits the government from taking private property – including intellectual property, such as proprietary data – without just compensation. FDA has consistently maintained the position that a manufacturer cannot directly rely on data from another without authorization from the owner.^{xv} Thus, biotechnology innovators have reasonable, investment-backed expectations that their data will not be shared. If this information is shared – by federal regulators – it is a government taking and requires just compensation.

Some may argue that a taking of innovator data is justified because it is in the public interest to lower healthcare costs and increase access to biologics. Without doubt, these are important public policy goals. But, we must not lose sight of the goal of finding new cures and developing new, innovative therapies. Thus, FDA, Congress, and the biotechnology industry should work together to ensure that innovation is encouraged and proprietary rights are respected. With these incentives, investors and companies will be willing to accept the bold risks associated with developing new biological products – in other words, to invest the “cure capital” necessary to discover and produce breakthrough treatments for serious diseases.

The European Union (EU) – which, admittedly, operates in a very different regulatory environment – has begun to tackle the issue of how a political community secures the right balance between innovator incentives and innovator rights, while also providing patients with as many market-based options as possible. The recently passed “pharmaceutical review” legislation in the EU illustrates one attempt.^{xvi} For newly approved products, the EU has established a protection period of eight years (during which no application for a generic version can be accepted), and a marketing protection period of ten years (during which no application for a generic version can be approved), which can be increased to eleven years if a new therapeutic indication is approved. These data and market exclusivity provisions represent an increase over the previous protections that existed in most European nations, and represent a careful balance between the rights and opportunities of innovator and follow-on companies, in a regulatory environment that – historically – has had less robust trade secret protections and fewer procedural rights than in the United States.^{xvii}

We must commit to a deliberate examination of the incentives that drive our industry, so that we can preserve our position as the seat of pharmaceutical and biotechnology innovation.

VIII. A STRUCTURED PROCESS IS NEEDED TO ADDRESS THE SCIENCE

Patients deserve safe, effective, and affordable treatments. No cost savings, however, is worth placing patient safety at risk. Amgen is committed to

bringing new therapies to patients in the most efficient manner possible while keeping patient safety as the primary consideration. Thus, Amgen supports a process that explores the development of follow-on biologics, but only if there is a robust public process and clear, science-based legal authorization.

In particular, Amgen believes that:

- Patient safety is paramount;
- There is no such thing as a “generic” biologic because identity cannot be established with the innovator product;
- Pre-clinical and clinical data will need to be provided by a follow-on company, with a post-marketing safety commitment required;
- Immunogenicity is a serious concern and should be carefully evaluated;
- Follow-on biological products must be held to the same high standards of safety, efficacy, quality, and manufacturing requirements as innovator products to ensure safety and efficacy for patients; and
- Any follow-on biologic approval process must respect and encourage innovation.

Amgen also believes that as legislators, FDA, and the public begin to think about a follow-on approval pathway, we must start with the recognition that follow-on biologics are truly unique products – and not carbon copies. As discussed above, *follow-on biologics cannot be considered therapeutically equivalent to the innovator product* (as is possible for small-molecule drugs, where the active ingredients in such products may be regarded as copies). Instead, while one can think of follow-on biologics as expanding the number of options in the marketplace for patients and healthcare providers, and as adding to the therapeutic armamentarium, it does not give rise to a true generic system.

From that principle, a reasonable set of pre-conditions to regulatory approval of follow-on biologics will flow. For example, the development of a follow-on biologic approval pathway must begin with a structured, public process to first resolve the myriad scientific questions implicated by follow-on biologics. Thereafter, any regulatory scheme ultimately developed should be transparent, science-based, predictable, and product-specific. The standards that are developed should be established only after comment by all interested persons, including legislators, scientists, doctors, patient groups, innovator companies, and healthcare associations. Moreover, in the interest of transparency, and to ensure that the knowledge and experience of the industry and the scientific community is harnessed, it is imperative that a follow-on approval system allow for case-by-case *premarket* comment on the standards for specific categories of products. The science is simply too complex, and the patient safety risks too great, to proceed in any other way.

This is illustrated by recent developments in Europe. The “pharmaceutical review” legislation, discussed above, permits the European regulatory authorities to approve follow-on biologics, or “biosimilars.”^{xviii} The legislation is far from presenting a clear legal framework, however. Still unresolved are the critical issues of how much data will be required for the follow-on applicants, and the extent to which regulators can rely on innovator data contained in agency files to approve follow-on applications. Furthermore, although the EU determined that, because of the risk of immunogenicity and other safety problems, pre- and post-approval safety data, including immunology data, will always be required for follow-on products, it did not establish clear parameters for these tests. As a result of these unresolved issues, the European authorities have been urged to issue additional guidance documents, including product- or class-specific guidelines, which would offer more transparency to all stakeholders.

If we are to learn from this example, we will determine the relevant scientific and safety standards *before* implementing a sweeping approval process for follow-on biologics that, at this point, would raise more questions than it would answer. This process must include product-specific or category-specific opportunities for comment prior to review and approval of follow-on products. As well, adequate safety data *must* be provided in the pre-approval stage for any proposed follow-on biologic, and these clinical data should be adequate to evaluate the immunogenicity of the follow-on biologic in comparison with the innovator

product. In addition, robust post-marketing surveillance systems must be in place to monitor the safety aspects of the product.

Amgen supports competition among products proven to promote health. We believe that follow-on biologics, as new biologic products approved based on pre-clinical and clinical data substantiating their safety and efficacy, can expand physician and patient choice. Thus, once patent rights expire, and assuming remaining innovator rights are appropriately recognized and protected, we are open to the creation of a legal and regulatory framework for follow-on biologics. We are committed to working with regulatory authorities to provide any expertise that we can share in this ongoing process to expand patient access to more treatment options.

IX. CONCLUSION

It is Amgen's considered view that the present-day generic drug paradigm cannot be applied directly to biologics. This is based on the fundamental differences between small-molecule drugs and biologics, including size, structure, and sensitivity to manufacturing processes. Most importantly, follow-on biologics raise the possibility of serious immunogenicity responses in patients, and these reactions are extremely difficult to predict. Thus, we believe it is imprudent, if not dangerous, for one manufacturer to receive approval for a biological product based solely on the clinical data produced by another manufacturer. Such reliance, without authorization by the data owner, would negate trade secret rights and pose

a compelling question under the Fifth Amendment. In addition, an approval system for follow-on products must preserve sufficient incentives for innovative organizations to invest in the continued research and development of new, life-saving therapies.

Amgen believes we should work together to explore whether a viable follow-on paradigm can be developed that would, as a matter of science, allow one sponsor to utilize analytical testing to demonstrate basic similarity, to apply an appropriate but flexible standard to establish efficacy, and to conduct robust pre- and post-market studies to assure safety. Even then, however, it would be inappropriate as a scientific and medical matter to consider the follow-on product to be the same or identical to, substitutable for, or interchangeable with, another sponsor's biological product.

The specific standards by which follow-on products should be tested and approved should be determined through a structured public process, with input from all relevant stakeholders, including the medical and scientific communities. If these stakeholders, together with Congress and FDA, commit to put the patient first, base decisions on sound science, and respect innovator rights, we believe a sensible policy regarding follow-on biological products will result.

Thank you for the opportunity to discuss these important issues with you, and I will be happy to answer any questions you may have.

ⁱ Ernst & Young, *Resurgence: The Americas Perspective on Global Biotechnology Report 2004*.

ⁱⁱ It is important to note that *before* Congress passed Hatch-Waxman, FDA had extensive experience implementing generic drug reviews for small molecule drugs under several different regulatory programs, including the Drug Efficacy Study Implementation (DESI) program and the agency's then-existing "paper NDA" process.

ⁱⁱⁱ See Johnson & Johnson Pharmaceutical Research and Development, Company News, Summary of PRCA Case Reports, at <http://www.jnjpharmarnd.com/company/news.html>.

^{iv} Biotechnology Industry Organization (BIO), Biotechnology Industry Statistics, at <http://www.bio.org/er/statistics.asp>.

^v The Industrial College of the Armed Forces, *Industry Studies 2002 – Biotechnology*, at <http://www.ndu.edu/ica/industry/IS2002/2002%20Biotechnology.htm>.

^{vi} DiMasi, *et al.*, Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at \$802 Million [news release] (Nov. 30, 2001). Notably, more recent studies have estimated drug development costs to be even higher. See DiMasi, *et al.*, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. OF HEALTH ECON. 151, 181 (2003) (placing pre-approved capitalized cost of developing a drug whose R&D is initiated in 2001 at \$1.9 billion); M. Uehling, *New Drug Costs Sky-High: \$1.7B*, BIO-IT WORLD (Jan. 12, 2004), available at www.bio-itworld.com/news/011204_report4132.html (reporting study by consulting firm Bain & Co. finding cost of developing one drug to be \$1.7 billion); see also FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004) (citing \$1.7 billion figure).

^{vii} Carey Sargent and Kim Frick, *Drugmakers in Europe Worry over Losing Talent*, The Philadelphia Inquirer, May 30, 2004.

^{viii} BIO, Biotechnology Industry Facts (1993-2003), at www.bio.org/speeches/pubs/er/statistics.asp.

^{ix} See *Deconstructing De-risking*, BioCentury (June 7, 2004) (discussing risks associated with biotechnology research and development).

^x Carol Rados, FDA Consumer Magazine, *Orphan Products: Hope for People with Rare Diseases* (Nov.-Dec. 2003), at http://www.fda.gov/fdac/features/2003/603_orphan.html.

^{xi} *Id.*

^{xii} *Id.*

^{xiii} Similar positive results were reached through the pediatric exclusivity provisions created by the Food and Drug Administration Modernization Act of 1997 (renewed and extended through 2007 under the Best Pharmaceuticals for Children Act, Pub. L. 107-109, January 3, 2001).

^{xiv} "Follow-On" Biologics Guidance Will Limit Use of Data to "Public Domain," The Pink Sheet (May 10, 2004) (quoting CDER acting Director Steven Galson, M.D.).

^{xv} See, e.g., Defendants' Memorandum in Support of Motion to Dismiss or, in the Alternative, for Summary Judgment, *Tri-Bio Laboratories v. FDA*, Civil No. CV-86-0083 (M.D. Pa., filed Apr. 3,

1986) at 62. In its brief arguing that the agency correctly refused to approve Tri-Bio's product based on published and unpublished safety and effectiveness data related to another manufacturer's product, FDA observed: "Since 1938, FDA has consistently taken the position that unpublished safety and effectiveness data submitted as part of an NADA or NDA are confidential, proprietary information which can not, except in very limited circumstances . . . , be released to the public or used to support another manufacturer's application." See also *"Follow-On" Biologics Guidance Will Limit Use of Data to "Public Domain"* ("FDA does not have the legal authority to reference information in an innovator company's BLA submission.").

^{xvi} This new legislation creates a unified standard for data exclusivity protection in EU Member States. Data exclusivity laws prevent regulators from reviewing or processing a generic manufacturer's abridged marketing application that references the first innovator's clinical safety and effectiveness data in the original application for a set period of time after the approval of the first product's marketing application. Until that period of data exclusivity runs out, neither the generic company nor the regulating body may rely upon the innovator's data to approve a generic version of the drug. Prior to the pharmaceutical review legislation, the periods of data exclusivity varied in Europe from country to country, generally ranging from six to ten years. The new legislation creates a harmonized ten-year period of exclusivity for all approvals in all Member States. The new EU law also changed certain patent provisions, and established basic governing principles regarding the approval of follow-on products. The EU has not published any product-specific guidances, however; as such, the amount and type of data that will be required for any future follow-on product remains unclear. For more information on the pharmaceutical review legislation, see Ludger Wess, *Ground rules for data protection, biogenerics*, BioCentury (Dec. 22, 2003); Steve De Bonvoisin, *Europe Approves New Set of Rules on Generic Drugs*, The Wall Street Journal Europe (Dec. 18, 2003).

^{xvii} Notably, these factors have led to markedly less investment in pharmaceutical research and development in Europe, and higher drug costs in the United States. See Jim Gilbert and Paul Rosenberg, *Imbalanced Innovation: The High Cost of Europe's "Free Ride,"* In Vivo magazine (March 2004), at www.bain.com.

^{xviii} A regulatory pathway for "biosimilar" products was initiated by a June 2003 European Commission Directive. The new 2004 pharmaceutical review legislation codifies and expands this prior law, and permits the European Medicines Agency to approve biosimilar products. Many of the standards regarding the type and amount of data that will be required for any such approval were left open, to be determined on a case-by-case basis. For more information, see The European Agency for the Evaluation of Medicinal Products, *Guideline on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues* (Dec. 11, 2003), available at <http://www.emea.eu.int/pdfs/human/bwp/320700en.pdf>, and *Guideline on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Active Substance, Non-Clinical and Clinical Issues* (Dec. 17, 2003), at <http://www.emea.eu.int/pdfs/human/ewp/309702en.pdf>; see also Wess, *Ground rules for data protection, biogenerics*; De Bonvoisin, *Europe Approves New Set of Rules on Generic Drugs*.



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**Establishing a Regulatory Pathway for Generic
Biotechnology Pharmaceuticals**

Testimony Before the Senate Judiciary Committee

June 23, 2004

Carole Ben-Maimon, M.D.
President & Chief Operating Officer,
Barr Research, Inc.



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**Establishing a Regulatory Pathway for Generic
Biotechnology Pharmaceuticals**

**Carole Ben-Maimon, M.D.
President & Chief Operating Officer**

Barr Research, Inc.

Senator Hatch. Honorable Members of the Senate Judiciary Committee. I am Carole Ben-Maimon, M.D., President and Chief Operating Officer of Barr Research, Inc., the proprietary products research and development division of Barr Pharmaceuticals, Inc., a leading U.S. specialty pharmaceutical company that markets more than 100 generic and proprietary products. I am a physician, board certified in Internal Medicine, and a mother of three. Prior to working at Barr, I was responsible for both generic and proprietary research and development with Teva Pharmaceuticals. I also spent two and one-half years as Chairman of the Generic Pharmaceutical Association.

My experience as a physician, and in both generic and proprietary drug development, has provided me a unique perspective on the pharmaceutical industry, a perspective that truly



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appreciates the value and contributions made by the passage of the Hatch/Waxman Act and a perspective that makes me an advocate for a legislative process that will permit the timely and efficient introduction of more affordable generic versions of biotechnology pharmaceutical products.

The issue before this committee today is not unlike that of 20 years ago, when Congress was crafting a legislative pathway for the efficient and timely approval of more affordable generic pharmaceutical products. Indeed, many of the arguments made in opposition to Hatch/Waxman 20 years ago are being, and will continue to be, made during this debate regarding generic biotech pharmaceuticals, namely: that “generic companies” lack the scientific sophistication to operate in this complex arena; that it is impossible to adequately characterize the innovator products; and that the safety and efficacy of generic biotech products can not be assured without full-blown clinical trials.

Fortunately for consumers and taxpayers, Senator Hatch and his colleagues had the wisdom and foresight to reject these arguments and approve the Hatch/Waxman Act. As a result, America’s generic pharmaceutical industry has been saving consumers tens of billions of dollars on pharmaceutical products each year. It is time for Congress to put these same principles to work in the area of biopharmaceutical products.



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To say that generic biotech products cannot be made flies in the face of the facts. The truth is, it is already being done in other parts of the world. Biogenerics are being developed, produced, and sold in countries such as Poland, China, and Lithuania. Given the long lead times for generic biopharmaceutical development, the United States is at substantial risk of losing our preeminence in this global field. The loss of a leadership position threatens that other countries will be dictating the standards for regulatory approval and the quality of these products. In addition, American scientists will lose the opportunity for the high-quality jobs that a robust American generic biopharmaceutical industry could bring to the United States.

Today, we urge Congress to begin the process of creating a regulatory pathway that will enable multiple pharmaceutical companies to develop and manufacture biotech pharmaceutical products in a cost-effective and cost competitive manner while still ensuring appropriate scientific standards for safety and efficacy. We ask Congress to pass legislation that will recognize and apply the current practice of comparability that enables biopharmaceutical manufacturers to change processes or manufacturing locations without conducting new safety and efficacy trials. We seek the establishment of a regulatory process that will enable the use of surrogate markers to ensure the safety and efficacy of generic biotech drugs, just as they do now under the Abbreviated New Drug Application process for traditional generic medicines. An abbreviated



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generic biotech pharmaceutical development process that accounts for scientific issues but acknowledges advances in scientific knowledge and understanding and thus limits duplication of development and bureaucracy is essential to ultimately limiting the investment required to develop cost-competitive generic biologic drug products. This will ensure that the American consumer reaps the benefits of these cost savings.

We are not asking this Committee or Congress to define the regulatory pathway today. Rather, we are asking Congress to begin the process of negotiating an efficient and cost-effective process for establishing a regulatory pathway that will be based on sound science and seek to re-establish America's position of leadership in this area. As with the approval of all pharmaceutical products, we are urging that this mechanism be reasonable and clearly tied to appropriate science that will establish safe and effective biotech pharmaceuticals.

Reality of Generic Biotech Drugs

As the United States begins the debate regarding the creation of a process for the approval of generic biotech drugs, we are in fact, playing catch-up to the rest of the world. While special interest groups attempt to convince Congress that generic pharmaceutical companies cannot overcome the hurdles to the development of these products, residents of other nations are already enjoying access to more affordable, generic biotech products.



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As an employee of Barr, my access to information about the availability of biopharmaceuticals at other drug companies is limited to what is publicly disclosed. But even a cursory examination demonstrates that a number of companies are already supplying generic biopharmaceuticals in other countries. These include Sicor, LG Chemicals, GeneMedix, Cangene, Rhein Biotech, Dr. Reddy's Laboratories, Wochart and Dragon Biotech. They are supplying human growth hormone, interferons, EPO, insulin and other biopharmaceutical products in markets such as Lithuania and other Eastern European markets, Mexico, China, Korea, India, Argentina, Egypt, Peru and Brazil.

The marketing of generic biotech products in other countries clearly demonstrates that the products are comparable and that safety is not an issue. The exposure of thousands of patients, without untoward effects, clearly demonstrates that these products are not only effective, but safe. With the necessary regulatory oversight, safety will be appropriately addressed and thus will not be an issue in the United States either.

There are also a number of biotech products that are already multisource in the United States. Insulin products are one example. These include Humalog, Humulin, and Humulin-L, from Eli Lilly; and NovoLog, Novolin, and Novolin L, from Aventis. The same is true for Human



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Growth Hormones, where Nutropin and Nutropin AQ, are made by Genentech Inc.; Humatrope by Eli Lilly, Genotropin by Pfizer; Norditropin by Novo Nordisk; and Serostim and Saizen by Serono Laboratories Inc. Each of these products required full development programs, costing consumers billions of dollars and exposing hundreds of patients to unnecessary clinical trials.

That multiple manufacturers are currently able to develop and produce these products on a large scale provides further confirmation that generic companies can and will develop and manufacture high-quality, equivalent generic biotech pharmaceuticals. Generic companies are no less capable than branded companies of applying state of the art science in manufacturing and product development. However, the regulatory process for generic biotech drugs can and should recognize that the safety and efficacy and many aspects of the safety of these products has already been established and thus significantly less additional testing is appropriate.

The argument that biotech drugs are so complex that they cannot be characterized ignores the fact that there are numerous highly sophisticated analytical methods available to all pharmaceutical companies, including generic companies. These methods permit the characterization of these complex proteins, and more methods are being developed. The argument that generic companies cannot characterize these very complex proteins is, in part, based on the mistaken impression that generic companies do not have the technological expertise or scientific, medical or clinical capabilities to safely develop generic biotech drugs.



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Advances over the past 20 years, both in the area of analytical methods and validation techniques have allowed companies to characterize their biologic drug products such that the impact of changes to process and cell lines can be evaluated and biologic drug products can be kept constant.

Generic companies have highly sophisticated R&D organizations and manufacturing capabilities, and most, in fact, already develop and market proprietary products just as brand companies do. While some drug products, both chemical and biotech, might be more complex than others, the vast majority can be fully characterized with currently available analytical methods. These analytical methods also can help identify and thus control any process-related impurities that are often found with biotechnology products. And continued advances in analytical methods will ultimately enable the characterization of all biotechnology products.

Finally, the argument is made that there is magic to the process of manufacturing biotech drugs. This may have been true when manufacturing processes were not validated and analytical methods were not advanced enough to characterize the final product. This is no longer the case. If it were, many of the products made by the various biotech manufacturers would not be available today. It is only the fact that these manufacturers have been able to utilize



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comparability protocols that has allowed them to make the necessary changes to processes and even cell lines required to allow them to supply these important drug products. In reality, biotech products can be fully characterized and compared analytically and biotech firms routinely justify process and site changes via comparability protocols.

In the United States, comparability is routinely being used to permit changes in manufacturing. When an innovator biotech company seeks changes in processes supporting the manufacture of their products, or seeks to change the manufacturing location of a product, comparability is the process by which the amended product is judged to provide the same clinical effect and safety profile. FDA does not require the innovator to conduct full-scale clinical trials to confirm the safety and efficacy of the product.

Utilizing surrogate markers to confirm that the amended drug will provide the same results is the very process that is used today in traditional pharmaceutical manufacturing to ensure the safety and efficacy of a generic drug. Under the current ANDA process, established by Hatch/Waxman Act 20 years ago, the safety of the innovator drug is established by the clinical trials conducted by the innovator prior to the approval of the New Drug Application. The generic applicant does not have to conduct clinical trials to prove safety and efficacy. Instead, the generic manufacturer must prove bioequivalence. Hatch/Waxman relied on the use of surrogate markers – namely



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plasma levels, the rate and extent of absorption of the drug product into the blood stream, to represent the efficacy and safety measure that is the basis for approval of generic drugs. Such a process, although employing different surrogate markers specific to each individual biologic product, is applicable to the approval of generic biotech products for many reasons. The use of these surrogate markers would allow for a more limited clinical program while still ensuring efficacy and safety.

Application of reasonable surrogates for measuring the efficacy and equivalence of generic drugs can and should be applied to generic biotech products, since it has been proven to be an effective and efficient measure of equivalence and has enabled the approval of safe and effective generic versions of traditional pharmaceutical products.

Compelling Need

America's pharmaceutical biotechnology industry represents one of the most successful and fastest growing segments of U.S. healthcare. Ten years ago, revenues for this industry were approximately \$8 billion. According to IMS, the international pharmaceutical data monitoring service, when you compare 2003 to 2002, the pharmaceutical biotech industry enjoyed revenue growth in excess of 22%, compared to 11% for the total market. By 2010, analysts estimate that



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biotechnology product sales will exceed \$60 billion. Generic competition is essential to control costs and continue to stimulate innovation.

More than 150 biotech drugs are on the market, including human insulin, interferons, human growth hormones and monoclonal antibodies. In the past year, more than 30 new drugs were approved, compared to only two in 1982. There are more than 370 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases including cancer, Alzheimer's disease, heart disease, multiple sclerosis, AIDs and arthritis.

Biologics are a major driver of increasing prescription drug costs. Six biotech pharmaceuticals – Procrit, Epogen, Neuposen, Intron - A, Humulin and Rituxan – generated sales of more than \$1 billion. And at least three new blockbusters are expected to join that list. The top three biotech pharmaceuticals: Neupogen, Epogen and Intron A cost patients \$23,098, \$10,348 and \$5,850 respectively, each year. Cerezyme, a drug indicated for the treatment of patients with Gaucher's disease, a rare disease resulting from the genetic deficiency of an enzyme, has annual patient costs of \$170,000. Although this drug treats a very limited number of patients, competition would surely drive these costs down and make this product more affordable for those who need it. As evidenced by these examples alone, generic competition for biotech pharmaceuticals has



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the potential to offer consumers dramatic and substantial savings, while also lowering America's healthcare bill.

As the number of these products grows, and the lifecycle of these products matures, the patents on these products expire. If Congress does not act now, Americans will continue to be faced with escalating drug prices while others, outside the U.S. reap the benefits of more affordable safe and effective prescription drug products. In addition, without the opportunity to develop and sell generic biotech products in the U.S., it is likely that all development and manufacturing activities will take place outside the U.S. and Americans will not have the opportunity to benefit from those jobs. Given the success of the Hatch/Waxman Act, it is essential that we insure timely competition for these very expensive biotechnology products ensuring cost competition, innovation and a U.S.-based industry.

Creating the Regulatory Pathways to Ensure Generic Competition

As with traditional generic pharmaceuticals before 1984, the obstacle standing between consumers and substantial savings on biotech drugs is the articulation of a regulatory process that will enable safe, effective, FDA-approved generic versions of biotech drugs to reach the marketplace following a well-defined, scientifically-based approval process.



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There are three issues here. The first is the lack of a generic approval process under the Public Health Service Act (PHSA). The second involves, what we believe to be, the mis-classification of some products approved under PHSA. It is our scientific contention that many of these products should rightly be reclassified under FDCA, which would open the door for possible generic drugs under Hatch/Waxman as it exists today. The third issue, or more a correction, is that some products were approved under the FDCA and these products do have a pathway for approval and should be reviewed through the ANDA process already defined under Hatch/Waxman but are currently not being reviewed as such by FDA.

We urge Congress to create legislation that will clearly define a pathway that enables FDA to review and approve all products on the basis of clinical science, on a case-by-case basis and without placing unnecessary requirements on generic companies which would result in unnecessary testing, increased expense, and limited access.

If generics are compelled to re-create the lengthy and expensive clinical studies required for the approval of the innovator drug, savings from generic biotech drugs will never be realized by American consumers as they currently are in other parts of the world. We urge Congress to ensure that the review process takes full advantage of all clinical data available, just as under the



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ANDA process, so that the development of generic biotech drugs will not require generic companies to re-create the science already established by the innovator.

Summary

In summary, the economic arguments for creating a process that will ensure timely generic competition for biotech drugs are compelling. We recognize the investment made by biotech drug developers in intellectual property, and endorse the need to ensure appropriate intellectual property protection and the ability to recoup their investment. As has been proven under the Hatch/Waxman Act, competition fuels innovation, and ensuring timely generic competition will ensure continued innovation in biotech drugs. We must preserve this incentive for innovation, but it is now time to provide the balance of competition to keep America's biotech innovators strong and growing. And we must learn from the lessons of Hatch/Waxman, and address, in advance, intellectual property issues that could, in the future, be used as a barrier to appropriate generic competition.

The pathway created under biotech generic legislation must enable and compel the FDA to review generic biotech applications in a manner that assures safety and efficacy. The standards for generic biotech drugs must be rigorous enough to ensure safety and effectiveness, and support consumer confidence in generic biotech drugs, but must not be permitted to require



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generic applicants to recreate large clinical studies that simply reinforce the scientific knowledge already available.

The science to create affordable generic biotech drugs exists today. It is being done in other countries. It is being done every time an innovator changes a manufacturing process or location and uses comparability to ensure the biotech drug will provide the same safety and efficacy. America is already losing the race to generic biotech products. But it is not too late. Congress can and must create the regulatory process that will help save consumers additional billions of dollars on prescription drug costs, by enabling the timely, efficient and cost-effective approval of generic versions of biotech drugs.

Thank you.

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STATEMENT

BY

LESTER M. CRAWFORD, D.V.M., Ph.D.

**ACTING COMMISSIONER OF FOOD AND DRUGS
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

“THE LAW OF BIOLOGIC MEDICINE”

BEFORE THE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

June 23, 2004

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, members of the committee, thank you for the opportunity to participate in today's hearing on the subject of follow-on biologics. I am Dr. Lester M. Crawford, Acting Commissioner, Food and Drug Administration (FDA or the Agency). I am honored to lead an agency whose mission is to protect the public health by assuring the safety and efficacy of our nation's human and veterinary drugs, human biological products, medical devices, human and animal food supply, cosmetics, and radiation emitting products.

EXECUTIVE SUMMARY

The enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) has been an unqualified success. Each year consumers save billions of dollars because lower cost generic drugs are on the market. In addition to approving generic drugs, FDA is examining other mechanisms to lower the cost of drug development and find ways to make the drug approval process faster, more certain and more affordable without compromising the thoroughness of drug review.

Because there are many unanswered scientific, legal and policy questions about follow-on versions of biologic products approved under section 351 of the Public Health Service (PHS) Act that must be explored, FDA plans to promote public dialogue on these

questions. We hope to address the challenging scientific and technical issues posed by such products, as well as to clarify the associated legal issues. Ultimately, the decision to proceed with a program for follow-on biologics regulated under section 351 rests with Congress; however, for biologic products regulated as drugs under section 505 of the Food, Drug, and Cosmetic (FD&C) Act, the Agency believes it can move forward with their consideration.

GREATER ACCESS TO MORE AFFORDABLE DRUGS

FDA and Congress share a great concern for senior citizens and other patients who have difficulty paying for prescription drugs. That is why the Administration worked with Congress to enact the new Medicare prescription drug law. And it is also why FDA has made it a priority to establish and expand programs that promote access to innovative treatments to help Americans live healthier lives and assure that Americans have access to medications and treatments that they can afford.

FDA has taken a number of significant steps to promote greater access to affordable prescription medications, including unprecedented steps to lower drug costs by helping to speed the development and approval of low-cost generic drugs. Generic drugs typically cost 50 to 70 percent less than their brand-name counterparts. According to the Congressional Budget Office, generic drugs save consumers an estimated \$8 to \$10 billion a year at retail pharmacies. The savings are even greater when the use of generics by hospitals is considered.

A. Hatch-Waxman

The Hatch-Waxman Amendments govern the generic drug approval process for human drugs approved under section 505 of the FD&C Act. The Hatch-Waxman Amendments were intended to balance two important public policy goals. First, Congress wanted to ensure that brand-name (also known as innovator) drug manufacturers would have meaningful incentives for research and development through patent protection and marketing exclusivity to enable them to recoup their investments in the development of valuable new drugs. Second, Congress sought to ensure that, once the statutory patent protection and marketing exclusivity for these new drugs expired, consumers would benefit from the rapid availability of lower priced generic versions of innovator drugs.

Since its enactment in 1984, Hatch-Waxman has governed the generic drug approval process. In general, the law has been working well. Since 1984, over 10,000 generic drugs have entered the market, and generics now account for close to 50 percent of prescriptions filled.

B. Recent Legislation in Response to Concerns

Over the past few years, Congress and the public focused attention on two key provisions of Hatch-Waxman. These grant 180 days of marketing exclusivity for certain generic drug applicants and provide a 30-month stay on generic approvals when there is patent infringement litigation. On June 18, 2003, FDA published

its final rule intended to speed access to and increase the availability of generic drugs by limiting the use of 30-month stays by brand-name drug sponsors and by clarifying the types of patents that must and must not be submitted to FDA for listing in the Orange Book.

The goal of FDA's rule was to improve access to generic drugs and lower prescription drug costs for millions of Americans. The changes will save Americans over \$35 billion in drug costs over the next 10 years and will also provide billions in savings for the Medicare and Medicaid programs. Elements of this rule were incorporated into the Medicare prescription drug law last year along with additional mechanisms to enhance generic competition.

C. Other FDA Efforts to Lower Drug Costs

FDA's objective is to enhance the ability of innovators, generic drug manufacturers and the Agency to achieve the goals embodied in Hatch-Waxman. The Medicare prescription drug law will enhance the Agency's efforts for taking additional steps to reduce drug costs by encouraging innovation and speeding up the drug development and approval process, while maintaining FDA's high standards for safety and effectiveness. Reforms in the generic approval process will generally shave months off the time to availability of generic drugs across-the-board. Similarly, new pathways for approving inhaled and topical generic drugs will potentially affect many products. This broad improvement in the

availability of new drugs and generic drugs will have a positive impact on all patients.

D. Resources for Generic Drug Review

For fiscal year 2004, Congress enacted an increase of \$8 million for FDA's generic drug program, the largest infusion of resources into this program since its inception. This increase in the generic drug budget enables FDA to hire additional expert staff to review generic drug applications more quickly and initiate targeted research to expand the range of generic drugs available to consumers. Improvements in the efficiency of review procedures have led to significant reductions in approval times for generic drugs since 2002 and will save consumers billions more by reducing the time for developing generic drugs and making them available. The Agency is now approving generic drugs at an average rate of one per day.

OTHER FDA INITIATIVES FOR AFFORDABLE DRUGS

In addition to our important responsibilities regarding generic drugs, the Agency has also taken steps to help improve the development process to help lower the cost of developing new drugs.

A. Lowering the Cost of Drug Development

FDA is continuing to improve the methods by which assistance and advice is provided to sponsors regarding what we believe are the best approaches to develop new therapies and maximize the prospects for swift FDA approval. These ongoing efforts are designed to provide sponsors with the best possible information and thus increase the efficiency of the development process. FDA has identified several priority disease areas, such as cancer, diabetes, obesity, and new technologies including gene therapy, pharmacogenomics and novel drug delivery systems that are good candidates for efforts to clarify regulatory pathways and clinical endpoints.

B. Advancing the Critical Path

On March 16, 2004, FDA issued a major report on medical product development. Known as the Critical Path Report, this document identifies the problems and potential solutions to the daunting task of ensuring that the unprecedented breakthroughs in medical science are demonstrated to be safe and effective for patients as quickly and inexpensively as possible. The report carefully examines the critical path of medical product development -- the crucial steps that determine whether and how quickly a medical discovery becomes a reliable medical treatment for patients. It also describes the unique opportunities for FDA to collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path more predictable, and less costly.

FDA will strive to turn the process of bringing these technologies to patients from a costly and time-consuming art form to a well-understood science. Our reviewers have a unique vantage point to understand the scientific challenges that cause delays and failures in product testing and manufacture. The enormous investment in biomedical science has yielded many promising technologies, ranging from engineered tissues to new kinds of biologics to genomics-based treatments, and we can help guide these technologies through the development pipeline and into the hands of the medical community.

THE IMPORTANCE OF INNOVATION

Medical innovation is a complex process, but one that can bring great value to patients. To realize the full benefits of medical innovation it is important to adopt policies that protect incentives to develop new drugs and medical devices.

Achieving this goal requires a delicate effort to strike a proper balance. Promoting innovation requires the right mix of incentives, safeguards, and effective regulation to secure maximum benefit from safe and effective new medical technologies, while assuring mechanisms for broad and equitable access to these new treatments. We will continue to realize the full benefits of medical innovation if we are thoughtful about achieving this balance. As Acting Commissioner of Food and Drugs, I am working to implement policies, initiatives, and regulatory improvements that reflect these important

goals in order to promote increased access to high quality, high value, safe and effective medical products.

PROTEINS REGULATED AS DRUGS OR BIOLOGICAL PRODUCTS

FDA has different statutory approval mechanisms for drugs and most biological products. I say “most” biological products because many biological products are also drugs, as that term is broadly defined in the FD&C Act. The FD&C Act defines drugs by their intended use, as “(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals” (FD&C Act, sec. 201(g)(1)). A biological product is defined, in relevant part, under the PHS Act, as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, or 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, sec 351(i)).

Traditionally, some natural source proteins have been regulated as drugs, including insulin, hyaluronidase, menotropins, and human growth hormones, while other natural source proteins, such as blood factors, are regulated as biological products. In the late 1970s and early 1980s, recombinant proteins and monoclonal antibodies began to be developed. These products were regulated by the Center for Drug Evaluation and Research (CDER) under the FD&C Act as drugs when they were hormones such as insulin and human growth hormones, and by the Center for Biologics Evaluation and

Research (CBER) under the PHS Act for cytokines or blood factors, such as factor 8 for the treatment of hemophilia. In 1993, CDER and CBER agreed to move all recombinant proteins and monoclonal antibodies to CBER except hormones such as insulin and human growth hormones, which remained regulated by CDER under the FD&C Act. In 2003, therapeutic products regulated by CBER were transferred to CDER, with no change to the applicable approval authority. Currently, some proteins are licensed under the PHS Act and some are approved under the FD&C Act.

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 most biological products under section 351 of the PHS Act. Full new drug applications (NDAs) under section 505 of the FD&C Act and biologics license applications (BLAs) under the PHS Act require submission of complete reports of clinical and animal data to support approval. For drugs approved under the FD&C Act, manufacturers can apply to FDA under section 505(j) of the FD&C Act for approval of generic versions of the brand products after the patent and other exclusivity periods expire. This process is known as the abbreviated new drug application (ANDA) process. Section 505(b)(2) also provides for approval of NDAs supported by literature or by FDA's earlier finding that a drug is safe and effective.

**A. Approval of Generic Versions of Drugs Approved under the
FD&C Act**

The ANDA process in section 505(j) was established through the 1984 Hatch-Waxman Amendments. This is an abbreviated approval mechanism for generic versions of drugs 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 bio-equivalent to the innovator drug, and must have the same dosage form, strength, route of administration, labeling, and conditions of use. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. By establishing that the drug product described in the ANDA is the same as the innovator drug product approved in the NDA, the ANDA applicant can rely on the Agency's finding of safety and effectiveness for the drug. Although generic drugs are essentially the same as their branded counterparts, they are typically sold at substantial discounts from the branded price.

Health professionals and consumers can be assured that FDA approved generic drugs have met the same rigid standards of quality, purity, and identity as the innovator drug. In addition, generic drugs must be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products.

In addition, the FD&C Act also contains an alternative mechanism through which an NDA sponsor can obtain approval of new drug products. This so-called

505(b)(2) mechanism permits a sponsor to rely on literature – or on the Agency’s finding of safety and effectiveness for an approved product – for approval of a drug product that differs from an approved innovator product (and thus cannot be a generic) or that requires additional human studies for approval.

Both the ANDA and 505(b)(2) approval processes incorporate consideration of the innovator’s intellectual property rights into the drug approval process. The patents listed with FDA by the innovator NDA holder at the time of NDA approval must be acknowledged by the ANDA or 505(b)(2) applicant, and approval will be delayed until patent disputes are resolved and statutory marketing exclusivity has expired.

B. Approval of Follow-on Versions of Biological Products Approved under the PHS Act

The FD&C Act provides the ANDA and 505(b)(2) abbreviated approval pathways for drugs approved under section 505 of that Act. However, the PHS Act has no similar provision. That is, unlike section 505 of the FD&C Act, there is no provision under the PHS Act for an abbreviated application that would permit approval of a “generic” or “follow-on” biologic based on the Agency’s earlier approval of another manufacturer’s application.

The approval of generic or follow-on protein and peptide products has both scientific and legal dimensions. First, as a scientific matter, FDA believes that

for some biologic products (primarily relatively simple peptide or protein products regulated under section 505 of the FD&C Act), science has progressed sufficiently that we are able to assess the degree of similarity or identity between the innovator and a follow-on product. The principle underlying such a determination is that the greater the degree of similarity or identity between two proteins, the greater the confidence that their clinical performance will be similar or the same. From a legal perspective, for products approved under section 505 of the FD&C Act, we also believe there is existing authority to allow applications for such products under section 505(b)(2) of the FD&C Act, relying on the earlier approval of the innovator product. In contrast, we do not believe such authority exists for follow-on biologics application under section 351 of the PHS Act that relies on the prior approval of the biological product or on data submitted by another sponsor.

NEXT STEPS

In recent years - and with increasing frequency - questions about generic or follow-on proteins have arisen in response to scientific advances, impending patent expirations, and the ability to better characterize and understand biological products.

Many drugs regulated under section 505 of the FD&C Act are small molecules. For these drugs, it has been possible to show scientifically that another product has the same active ingredient as the innovator product. On the other hand, because protein drug

products are large, complex molecules, derived from biological sources, generally it has not been possible to assess relative sameness with a high degree of confidence.

However, the science of characterization has progressed to the point where it is becoming possible to make such assessments for some products, and we expect that science will continue to progress.

Acknowledging scientific and legal limitations in this area, yet also recognizing the public health need to move forward to assist industry and make more products available to the public, FDA intends to conduct a public process to examine the scientific, and related issues regarding follow-on biologics. This process will ensure that scientific considerations and issues related to Agency authority are fully examined and that all interested parties have an opportunity for input.

CONCLUSION

FDA believes that follow-on proteins, like the advent of generic drugs, may hold the potential for greater access to therapies and meaningful savings for consumers. We acknowledge that approvals of follow-on versions of more complex products are likely still years away, and would require resolution of serious scientific, legal, and policy issues. Furthermore, we recognize that the limitations inherent in the authorities related to the PHS Act differ from the authorities available to consider some biologic products regulated as drugs under the FD&C Act. Yet we also believe that it is in the interest of the public health to provide meaningful opportunities for thoughtful public discourse on this subject as the science progresses. Today's hearing is an important part of that discussion and I thank Chairman Hatch for holding it.

**William Hancock, M.D.
Bradstreet Chair of Bioanalytical Chemistry
Northeastern University
Boston, MA**

Outline of Testimony

Introduction

Thank you for the opportunity to testify today on the issues around the production of follow-on biologicals (recombinant DNA or rDNA derived protein pharmaceuticals). My name is William S. Hancock, and I am Professor and Bradstreet Chair in Bioanalytical Chemistry at Northeastern University in Boston, Massachusetts. I am familiar with the significant scientific hurdles associated with manufacturing biological products from more than thirty years working in the area in academia, industry and government. Though my government service was brief, I served as a Visiting Scientist at the Food and Drug Administration's Bureau of Drugs in 1983. From 1985 to 1994, I worked on biological drug products at Genentech, one of the pioneers in this area, first as a staff scientist and later as Acting Director of Pharmacology. I have also held scientific positions at Hewlett Packard Laboratories and ThermoFinnigan Corporation, a maker of mass spectrometry instruments, where I served as Vice President of Proteomics from 2000 to 2002 before accepting my current position on the faculty of Northeastern University. I have authored or co-authored over 150 peer-reviewed books and articles, many dealing with issues regarding the characterization and manufacture of biologics. I thus appreciate the opportunity to share my thoughts with the Committee on this difficult but important subject.

Summary

I believe that there is a substantial scientific challenge (both analytical and non-analytical) to achieve the adequate characterization of any biotechnology product. Furthermore, I believe that the production of safe and effective follow-on biologicals is very difficult, if not impossible, in the near future. The following discussion will highlight the major differences between small molecule drug products and biologics which present the greatest scientific challenges for approval of follow-on biologics.

Outline of Testimony

1. Overview: Comparing scientific aspects of small molecule drugs and biologics

- Physical properties
- Structure and mechanism of action
- Manufacturing and product quality
 - Process, quality assurance
- Product safety aspects

2. Physical Characteristics

- Composition: drugs may be composed of dozens of atoms; biologics may be composed of millions of atoms
- Molecular Weight (Size): drugs may be measured in 100s of Daltons; biologics in 100's of KiloDaltons
- Structure: drugs can be described by a chemical formula that is fixed; biologics typically cannot be described by a single chemical formula
- Production: drugs are chemically synthesized by scientists according to a "cookbook"; biologics are synthesized by "organisms" (e.g., bacteria, mammalian cell culture)
- Mechanism: for drugs, the mechanism of action is usually understood; for biologics it is not always understood

3. Manufacturing and Product Quality

a. Making a small molecule drug vs making a biologic

- Starting Material: for drugs, it is chemicals; for biologics, it is DNA plasmid vector & cells or a whole animal
- Initial Process: for drugs, it is chemical reactions and synthesis; for biologics, it is transfection or insertion of DNA into a host organism
- Vessel for synthesis: for drugs, it is specialized glass and/or metal containers; for biologics, it is bacterial, insect, mammalian cells or whole animal
- Initial Product: for drugs, it is a highly purified chemical compound; for biologics, it is a cell lysate or cell culture medium
- Components: for drugs, the components of the product are defined; for biologics, the components typically are complex and undefined

b. Quality and GMP

- "Process controls" are a key element in defining product quality
 - Such controls are quite different for chemical and biologic manufacture
- Product vs process knowledge
 - For small molecule drugs, process knowledge is less important than product knowledge
 - For biologics, experience with process is essential for biologic manufacture - 'the process is the product'
- Contamination during manufacturing
 - Easily avoided for small molecule drugs; detectable; often removable

- For biologics, possibility of contamination with viruses & other adventitious agents; detection may be harder; removal impossible

c. Process “know how” for biologics

- Familiarity with production process essential for understanding of which changes affect final product and which do not
- Apparently small changes, such as a new batch of cells, can dramatically—and unpredictably—alter function of final product
- This experience can only be obtained over years of manufacturing

d. Analytical Testing

- Small Molecule Drugs
 - Simple physical & chemical methods
 - Precise composition & structure
- Biologics
 - Complex physical & chemical methods
 - Primary protein structure (sequence)
 - 3-dimensional structure – only sometimes
 - Protein modifications
 - Glycosylation
 - Phosphorylation
 - Prohibitively resource intensive to determine precisely
 - Biological products often a heterogeneous mix

4. Product Safety Aspects

Immunogenicity

- Small molecule drugs rarely elicit immune response
- Macromolecules (proteins) of biologic drugs are capable of triggering immune response with varying consequences
 - Antibodies may neutralize the molecule making it therapeutically ineffective
 - Rare but serious autoimmune responses can be life-threatening
 - Immunogenicity of biologic drugs is unpredictable, unforeseeable
 - Small changes in a macromolecule can completely shift its immunogenicity profile

5. Scientific and medical challenges with biologics

- Limits of Analytical Testing
 - For small molecule drugs, full characterization readily undertaken

- For biologics, full characterization technically impossible today
 - Quality, GMP considerations different than for small molecules
 - Process changes and access to innovator data
 - For small molecule drugs, the process does not define the product
 - For biologics, the process uniquely defines the product
 - Immunogenicity and Safety: An issue for biologics that is not present for small molecule drugs
6. **Final Thoughts**
- Biologic drugs are orders of magnitude more complex than small molecule drugs
 - Safety & efficacy of final product are exquisitely sensitive to small changes in process
 - It is difficult to impossible to predict the effect of these small changes—
experience counts
 - Potential for dramatic negative health consequences

Statement
United States Senate Committee on the Judiciary
The Law of Biologic Medicine
June 23, 2004

The Honorable Orrin Hatch
United States Senator, Utah

“The Law of Off-Patent Biopharmaceuticals”

Today, the Judiciary Committee will consider a complex subject area that involves law, economics, science and medicine.

The purpose of the hearing is simple — although the law and science surrounding these issues are not. We will explore some of the key issues concerning the legality, feasibility and advisability of creating a new, abbreviated regulatory pathway at the Food and Drug Administration for the review and approval of off-patent biological products.

First, for those of you who may not be sure what a biologic is, I would like to offer a simple working definition: Biological medicines are large complex protein molecules, derived from living cells, often by recombinant DNA technology. The area of biologics is of growing medical and economic importance. The biotechnology market posted a total of about \$30 billion in sales last year, which is expected to double to over \$60 billion by 2010.

We will see a concurrent explosion in the numbers of biologics; there are now over 150 FDA-approved products on the market, with an additional 350 in various stages of human clinical testing and over 1,000 others in the development pipeline.

But more important than commercial considerations, it is the hope of many that biological products, such as those that may one day be developed from embryonic stem cells, could lead to cures to many diseases that cannot be successfully treated today. Biopharmaceuticals appear to represent the future of medicine. For example, now that we have mapped the structure of the human genome, we are in position to unravel the mysteries of the function of human genes and the proteins they encode. Nothing less than a revolution in our understanding of human health and disease is well underway. I am proud of the fact that scientists at the Huntsman Cancer Institute at the University of Utah are helping to lead the way.

The old model of large patient population, small molecule medicine is giving way to large molecule, small patient population therapies. The day may even come when individualized therapies will become common. These developments will not occur overnight and without great effort and ingenuity and they will not be done on the cheap. One thing is certain: when medical breakthroughs occur, patients will want access to these new products and their families and third party-payers will want to pay as little as possible for them.

Experts remind us that this new wave of therapeutic protein molecules is more complex to discover, manufacture, and use than conventional small molecule drugs. We know that many of these new biological products tend to be more expensive than old-line chemically synthesized drugs. Some of these new wonder therapies cost over \$10,000 per year or per course of treatment. For example, human growth hormone can cost \$25,000 per year.

Cost factors alone compel a thorough examination and public discussion of the merits of developing a

fast track review and approval system that can reduce the price of biopharmaceuticals once patents expire. Moreover, from a regulatory reform perspective, it should always be the goal of government to employ the least burdensome regulatory approach without compromising other important considerations such as, in this case, patient safety and protection of intellectual property.

Former Commissioner of Food and Drugs and current CMS Administrator, Dr. Mark McClellan -- who took time from his busy schedule last week to visit Utah and meet with me and other Utahns on the new Medicare drug program -- has recognized the confluence of medical, economic, and regulatory forces at play.

Our society can ill-afford to avoid a debate over the proper regulation of follow-on biologics. We simply cannot sustain over time programs such as Medicare unless we seriously explore what steps might prudently be taken to end an FDA regulatory system that effectively acts as a secondary patent for off-patent biological products.

Patient safety and product efficacy must remain of the forefront of this discussion. The task before policymakers is to consider how to maintain product safety and efficacy as we consider ways to eliminate unnecessary regulatory hoops for off-patent biological product license applications.

I will stipulate that it will be difficult to manufacture some generic equivalents of off-patent biologicals. Some products will no doubt be more difficult than others to reverse engineer. There will be technical issue galore. Some may actually prove impossible to duplicate without trade secret information but, from what I have heard, many products will be able to be safely duplicated.

I believe that many, if not all, follow-on biological will require at least some form of human clinical testing. I also believe that the federal government would be wise to consider providing taxpayer funding for the development of process validation guidelines that will help establish the critical manufacturing steps and assay parameters for medically or commercially significant off-patent biological products.

I think it would be wise to consider commissioning or otherwise sanctioning studies by organizations such as the United States Pharmacopeia or the Institute of Medicine, in collaboration with the FDA and other interested parties, to identify and address the technical issues that need to be resolved in order to fast track approvals for off-patent biopharmaceuticals.

I have known and worked with Acting Commissioner of Food and Drugs Crawford for many years and look forward to working with him and other experts at the FDA on this important issue. I know that Dr. Crawford will make this an important priority and look forward to seeing the draft guidelines when they are issued later this year. I trust that Chief Counsel Dan Troy and Deputy Commissioner Amit Sachdev and Liz Dickinson and Jerilyn Dupont will provide sound legal and policy advice.

As a co-author of the Drug Price Competition and Patent Term Restoration Act of 1984, I firmly believe that whatever we do on the legislative front should observe a principle of attempting to balance incentives for both pioneer and generic drug firms. While I am all for rolling up our sleeves to work to help develop an abbreviated approval system for off-patent biologics, we must be properly respectful of the intellectual property of research-based firms because this is what undergirds the whole pharmaceutical enterprise.

As we proceed into this new era of drug discovery, it is important to ask whether our current intellectual property laws relating to pharmaceutical research and development are adequate to

promote the large molecule, small patient population medicine of the future? For example, I have long thought the way we treat process patents under Hatch-Waxman should be re-examined in this new era of patient population medicine in which process patents will become more important in which the relative importance of such patents will increase.

Difficult policy questions will crop up in a very difficult climate for the research-based pharmaceutical industry, everyone's favorite whipping boy in an election year. Senator Lieberman and I have advanced an aggressive set of private sector incentives in our bipartisan bioterrorism bill. I plan to hold a hearing on the Lieberman-Hatch Bioterrorism bill, and we urge all interested parties to review the IP provisions of this legislation.

Twenty years ago, we faced many challenges in fairly balancing the incentives and various interests when we came together on Hatch-Waxman. Frankly, I recognize that many in the biotechnology industry believe that the creation of a fast track approval process for off-patent biologics is the worst nightmare of a highly competitive, inherently risky industry struggling to attract the capital necessary to bring new products through FDA approval and to the marketplace.

Let me close by suggesting an alternative, and perhaps preferable, strategy to scorched earth litigation. Rather than just saying no, please consider engaging in a constructive public policy dialogue that focuses on identifying the legitimate scientific and legal obstacles that must be overcome to create a fast track approval system for off-patent biologics. At the same time, come forward with ideas that will improve the legal environment for pioneer biotechnology firms.

That is what we did in 1984 and that is what we can do again today if we all work together on follow-on biologics and other matters. If we have the right balance in the law, the American public only stands to benefit.

Statement
United States Senate Committee on the Judiciary
The Law of Biologic Medicine
June 23, 2004

The Honorable Patrick Leahy
United States Senator, Vermont

Hearing on "The Law of Biologic Medicine"
June 23, 2004

Mr. Chairman, I appreciate your holding a hearing on this important topic.

Biologic therapies fight life-threatening diseases and disorders. In many cases, these therapies are orders of magnitude more effective than drug therapies.

The most famous biologic treatment saved millions of lives and has eradicated epidemics which, in the 1930s and 40s, created mass panics each summer.

Indeed, the first major outbreak of polio in the United States was in Vermont during the summer of 1894.

Rather than using the powerful tools of molecular biology, physicians back then willy-nilly came up with therapies, such as concocting an emulsion from the ground-up spinal cords of polio-infected monkeys. They then added other chemicals to that witches' brew. One researcher, Dr. Jonas Salk, added formalin to the mix, and the rest is history.

Now, research for new biologic therapies is no longer an endless guessing game. Potent new technologies hold the promise to develop completely new classes of therapies to prevent, treat or cure otherwise inevitable, untreatable and incurable diseases.

These new technologies are being focused on the horrors of cancer, cystic fibrosis, hemophilia, AIDS, Alzheimer's, and multiple sclerosis, just to name a few.

For example, breakthrough biologic therapies such as Avastin starve cancer tumors of the blood supply they need to grow. Activase is used to greatly reduce the otherwise permanent disabling effects of strokes in adults.

Biologic technologies also hold out the best hope for those suffering from certain rare diseases that afflict 25 million Americans, including 58,000 Vermonters.

However, biologic therapeutics often cost far more than traditional drugs. One reason for this is that biologics are a lot more complex chemically and are more difficult to manufacture.

It is important that we address this approval issue now because the patents on many biologic therapies will expire in the next few years.

With respect to drugs, Chairman Hatch and Congressman Waxman played crucial roles in developing a fast-track process to get less expensive, safe and effective generic drug alternatives into the market place under the Hatch-Waxman law.

But a clear fast-track pathway does not exist for biologic therapies under current law.

So the critical question we face today is, should Congress design a fast-track process for generic versions of these biologic innovations?

My own answer is “yes,” but only if what we do is based on sound science, if these alternative therapies are safe and effective, if they will help prevent shortages, and if these biologics would provide less expensive, yet potent, alternatives for consumers.

I know that generic biologics are now available in Eastern Europe and Asia. Many point out that these biologics have been safe and effective and are less expensive than the original products in those countries. Others urge that we can not be sure of the safety or legality of these products made overseas.

It may be that a sliding-scale approach is needed for the United States. The level of scrutiny should intensify with the increasing:

- complexity of the molecules involved;
- sensitivity of the formulation process; and
- the risks of deviation from the patented product.

Science must rule this decision – not politics, not greed, not the clout of powerful vested interests. We need to do the right thing for the millions of affected families.

I hope that we can work together to find a faster way to get more of these valuable therapies available, at lower prices, to consumers, without sacrificing safety.

I hope that all stakeholders will participate in this process. The testimonies of Dr. Ben-Maimon and David Beier present a useful point and counter-point on both sides of this issue. Mr. Beier also raises complex trade-secret issues.

The bottom line is that any such legislation will require a careful balancing of interests and recognition of patent and trade secret rights.

We need to work together for the families who could be helped by this approach. I am therefore pleased to begin our consideration of this important issue with today’s hearing, and I welcome the testimony of our distinguished panelists.

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TESTIMONY OF WILLIAM B. SCHULTZ

On Behalf Of The Generic Pharmaceutical Association

Before The Senate Judiciary Committee

Hearing On The Law Of Biologic Medicine

June 23, 2004

Chairman Hatch and Members of the Committee. Thank you for the opportunity to testify on the issue of access to affordable biopharmaceuticals. I am here today on behalf of the Generic Pharmaceutical Association (“GPhA”), the trade association whose 120 members produce more than 90% of all generic drugs sold in the United States.

Senator Hatch, for more than 20 years you have been a leader in Congress in efforts to ensure greater public access to affordable drug products. Your instrumental role in the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act”) established the regulatory framework for generic versions of brand drugs regulated under the Federal Food, Drug, and Cosmetic Act (“FDCA”).

It is fitting that you have taken the initiative to begin the discussion on how Americans can have access to generic versions of today’s promising biotech medicines, which are manufactured by processes using biological organisms (or microorganisms). These drug products are referred to as “biopharmaceuticals.”

As we all know, the Hatch-Waxman Act has been tremendously successful in providing Americans with access to affordable pharmaceuticals. As a result of this law, today there are more than 7,600 generic versions of the approximately 10,375 FDA-approved pharmaceuticals.¹ And, more generic pharmaceuticals are approved every day. Let’s take a closer look at the progress of affordable generics under Hatch/Waxman.

¹ FDA Orange Book.

In 1984, generic drugs accounted for less than nineteen (19) percent of all prescriptions filled. Today, generic drugs represent more than fifty-one (51) percent of all prescriptions dispensed in the United States.² In addition, even though generics account for more than half of prescriptions dispensed, generics account for less than eight cents of every dollar spent on prescription drugs.³ And of course the federal government, which purchases roughly 12% of all prescription drugs (costing nearly \$21 billion in 2002) is the biggest consumer of all, and reaps enormous savings from generic drugs.⁴

Passage of the Hatch-Waxman Act came at a critical juncture in America's efforts to make drug products affordable and accessible to consumers. In 1984, we were at a crossroads in terms of drug pricing and innovation in this country. At that time, we had a flourishing pharmaceutical industry that was developing innovative products, but was charging monopoly prices even after patents had expired. The Hatch-Waxman Act accordingly struck a balance between encouraging innovation and facilitating access to affordable medicines. And, by all measures, the 1984 Act has been successful on both fronts. The brand pharmaceutical industry has grown from a \$19 billion industry in 1984, to a more than \$200 billion industry in 2003. Simultaneously, the generic pharmaceutical industry has grown to where today over seven thousand FDA-approved generic pharmaceuticals are on the market, saving this Nation's health care system tens of billions of dollars each year.

² Warren Strugrath, "Carving a Niche in Generic Drugs," THE NEW YORK TIMES, April 13, 2003, p. 6, col. 2.; Gardiner Harris, "Drug Firms' 'Bad Year' Wasn't So Bad," THE WALL STREET JOURNAL, February 21, 2003.

³ January 2003 IMS Doug Long Presentation.

⁴ Table 3: National Health Expenditures, By Source of Funds and Type of Expenditure: Selected Calendar Years 1997-2002, Center for Medicare and Medicaid Services, at <http://www.cms.hhs.gov/statistics/nhe/historical/t3.asp>.

We are at a similar crossroads today with respect to generic biopharmaceuticals as we were in 1984 with respect to traditional pharmaceuticals. The generic pharmaceutical industry is convinced that the savings resulting from competition, and the incentive for brand companies to invest in innovation that also results in more new groundbreaking therapies, can be similarly applied to the biopharmaceutical industry.

As I turn to the important policy issues associated with access to affordable biopharmaceuticals, I would first like to note that, while the generic industry and FDA currently are engaged in discussions over the proper nomenclature for these products, for purposes of this hearing, we are referring to these products as “generic biopharmaceuticals.”

Over the last 20 years, scientific advances have made the biotechnology industry an integral part of the pharmaceutical industry, producing essential, safe and effective biopharmaceutical products that meet critical medical needs for severely debilitating and life-threatening illnesses, such as multiple sclerosis, rheumatoid arthritis, and enzyme deficiencies. Historically, biological products have been products such as vaccines, blood, and anti-toxins regulated under the Public Health Service Act (“PHS Act”). Today, while many biopharmaceuticals are approved under the PHS Act, others are biotech products are approved under the Federal Food, Drug, and Cosmetic Act.

In 1984, the biopharmaceutical industry was still in its infancy, with only one biopharmaceutical product on the market. Today, more than 150 biotech drugs are on the market, including human insulin, interferons, human growth hormones and monoclonal antibodies. In the past year alone,

more than 30 new biopharmaceutical drugs were approved. More than 600 products are in development and new products are being reviewed and approved by the FDA on a regular basis.⁵

America's biopharmaceutical industry accordingly represents one of the most successful and fastest growing segments of U.S. healthcare. From 2002 to 2003, the pharmaceutical biotech industry enjoyed revenue growth in excess of 22%, compared to 11% for the total pharmaceutical market.⁶ In 2003, biotechnology products accounted for more than \$33 billion in sales, or 12% of total pharmaceutical sales in contrast to the \$ 8 billion sector of 1993.⁷ Moreover, analysts estimate that by 2010 biologic sales will exceed \$60 billion.⁸

Biologics are a major driver of increasing prescription drug costs. In 2003, six biotech pharmaceuticals -- Procrit, Epogen, Neupogen, Intron-A, Humulin and Rituxan -- generated sales of more than \$9.5 billion. The top three biotech pharmaceuticals: Neupogen, Epogen and Intron A cost at least \$15,000, \$10,000 and \$22,000 per patient, per year, respectively.⁹ Moreover, Cerezyme, a biopharmaceutical drug product for an enzyme deficiency, costs over \$170,000 per patient, per year.¹⁰ This drug was approved in 1994, and the product's cost will remain high in years to come without price competition. As evidenced by these examples, generic competition for biopharmaceuticals has the potential to offer consumers dramatic and substantial savings, while also lowering America's overall healthcare bill.

⁵ 2002 In Perspective, Venture Capital Insight, Ernst & Young, citing BioCentury; WASHINGTON DRUG LETTER, March 8, 2004.

⁶ IMS, International Pharmaceutical Data Service.

⁷ *Id.*

⁸ Table 7: Domestic Sales and Abroad, PhRMA Member Companies: 1970-2003, Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2004.

⁹ See DESERET NEWS, December 15, 2002; REUTERS NEWS, April 28, 2002; ST. PETERSBURG TIMES, July 22, 2003.

¹⁰ THE NEWS & OBSERVER, May 13, 2003.

Currently, there are more than a dozen biopharmaceuticals for which U.S. patents have expired, or will expire within the next two years.¹¹ This number will only continue to increase as the pharmaceutical industry continues to develop more biotech products. The time is now to ensure competition for these very expensive biopharmaceutical products. Competition will not only result in consumers having access to more affordable prescription drug products, but also foster innovation in the biopharmaceutical industry: a win – win situation for all.

In short, Mr. Chairman, today we are at a crossroads similar to the crossroads Congress faced in 1984. In 1984, as now, there were a significant number of brand drugs on the market for which patents had expired but for which there was no generic competition. Today is roughly 20 years since the first biopharmaceuticals were approved. As was true for post-1962 chemical drugs in 1984, even where patents have expired, FDA requirements are a regulatory barrier to competition and lower drug prices. And just as in 1984, the biotechnology industry adamantly opposes competition, even after their patents have expired.

In 1984, FDA and Congress recognized that a new regulatory system for generic drugs made sense. Today, it is widely recognized that a program providing for the approval of generic biopharmaceuticals makes sense as well. As former FDA Commissioner Mark McClellan recognized this year, “we do believe that the science may be adequate now to proceed on several relatively simple biologics that were approved as NDAs, and hence are subject to Hatch-Waxman laws.”¹² The same science recognized by Dr. McClellan also applies to products approved under the Public Health Service Act.

¹¹ "Generic Biologics: The Next Frontier," ABN-AMBRO (2001).

¹² McClellan Speech Before the GPhA Annual Meeting, March 18, 2004.

Even as we are debating how to codify a regulatory paradigm for generic biopharmaceuticals, other countries are actively implementing such programs, including countries in the EU, Asia and Latin America. In fact, the EU issued guidance three years ago to assist the industry in bringing generic biopharmaceuticals to the market. At least one company in our membership has been distributing generic biopharmaceuticals for over a decade in at least 15 countries around the world. These products have demonstrated safety and efficacy. As the world leader in pharmaceutical development, the U.S. should be willing to take on a leadership role in the development of a viable framework for generic biopharmaceuticals. If Congress does not act now, Americans will continue to be faced with escalating drug prices, while others reap the benefits of affordable biopharmaceutical products.

The brand companies have argued that it is not even worth debating the legal contours of a regulatory system for generic biopharmaceuticals because, as a matter of science, no such system is possible. We disagree. First, as FDA has recognized, there is already a scientific basis for some generic biopharmaceuticals. In addition, as the brand companies are well aware, when a company is given an incentive to develop new technologies or scientific approaches to seemingly intractable problems, innovation that surmounts these obstacles will usually follow. Thus, it is crucial that a regulatory system for generic biopharmaceuticals be codified that creates incentives for generic companies to engage in the research and development of generic biopharmaceuticals. With these incentives in place, we are confident that many of the allegedly insurmountable scientific obstacles to generic biopharmaceuticals will soon fall by the wayside.

We recognize that FDA is not likely to act without direction from Congress in the form of legislation. GPhA believes FDA currently has the legal authority to approve generic biopharmaceuticals with less than the full set of pre-clinical and clinical data required for the approval of the brand product. This is not the place to set out an elaborate legal analysis, but there are a number of bases for such authority. First, certain biopharmaceuticals, such as Insulin and Human Growth Hormone, are *already* regulated under the FDCA and are subject to the Hatch-Waxman Amendments. To the extent that generic biopharmaceuticals may not qualify for approval under the basic generic approval provision in the statute (section 505(j) of the FDCA) because simple blood level studies are not sufficient to establish equivalence, they would qualify under a separate provision of the Act, known as “section 505(b)(2).”¹³

Under section 505(b)(2), FDA can rely on its earlier approval decision of the brand product, and then require additional data, as appropriate, to confirm that the generic product is safe and effective. FDA recently upheld the use of section 505(b)(2) in this regard.¹⁴ The brand-name pharmaceutical industry disagrees with this interpretation of section 505(b)(2). In response, I would point out that this has been FDA’s consistent interpretation of the law since it began issuing regulations to implement the Hatch-Waxman Act.

It is true that today the FDA regulates most biopharmaceuticals under the Public Health Service Act,¹⁵ which, as previously discussed, is not part of the Hatch-Waxman regime. But the Public Health Service Act has for many years contained a provision stating that nothing in that Act shall affect the FDA’s jurisdiction under the FDCA, and it is clear that FDA could regulate all

¹³ 21 U.S.C. § § 355(b)(2), 355(j).

¹⁴ FDA response to Pfizer citizen petition (October 14, 2003).

biopharmaceuticals under the FDCA, as it had chosen to do for insulin and human growth hormone.¹⁶ In fact, Congress made this point explicit in 1997 when, in the Food and Drug Administration Modernization Act, it changed the PHS Act to state directly that the FDCA applies to biological products subject to regulation under the PHS Act.¹⁷

Precedent exists for the approval of biopharmaceuticals with reduced pre-clinical and clinical data packages under the PHS Act. These biotech products include Hepatitis B vaccines and the Hemophilus influenza type B vaccine, among others. It is our understanding that allergenic extracts, crude biological products derived from plants and animals also have been approved under this legal mechanism with limited pre-clinical and clinical data. In addition, FDA allows for interchangeability for products approved under this Act. For example, the FDA-approved labeling for GlaxoSmithKline's yeast-derived Hepatitis B vaccine states that this product is comparable and interchangeable to other Hepatitis B vaccines derived from yeast and blood plasma. This interchangeability allows the health care practitioner to select among a wide variety of Hepatitis B vaccines produced from various cell sources and manufacturing processes to complete a course of immunization in healthy patients, including children. Thus, FDA has approved biopharmaceutical products under the PHS Act which are supported by abridged pre-clinical and clinical data sets, and, in at least one instance, has deemed the product interchangeable with other comparable brand products.

A principal argument advanced by the brand-name companies in opposition to a system for the approval of generic biopharmaceuticals is that such a system would be unconstitutional because

¹⁵ 42 U.S.C. § 262.

¹⁶ See 42 U.S.C. § 262(f) (1996).

it would amount to a taking of their property without just compensation. In fact, one brand-name company, Genentech, recently filed a citizen petition with the FDA in which it made the extraordinary argument that the FDA could not even issue guidance on data requirements for the marketing of generic biopharmaceuticals.¹⁸ As I understand it, Genentech's argument is that FDA has gained certain expertise after reviewing submissions by Genentech and others and that, regardless of whether it releases the actual information supplied by the brand companies, it may not even use the experience and knowledge it has previously gained in the review process to draft a guidance document on data requirements for generic biopharmaceuticals. Of course, this argument is counter to FDA's long-standing position on guidance documents. That is, an FDA guidance "represents FDA's current thinking" on a specific topic. This "current thinking" represents the Agency's cumulative knowledge to advance science. Even if FDA were to release the information after the brand company's patents had expired, release of such information would not constitute an unconstitutional taking under controlling Supreme Court case law. GPhA is having a thorough constitutional analysis prepared on the taking issue and will submit it to interested members once it is prepared.

Nevertheless, I want to emphasize that in case of the use of section 505(b)(2) of the FDCA, the FDA is simply proposing to reduce the data requirements for generic biopharmaceuticals based on its approval of the brand product. It would be relying on the knowledge gained of the brand product, but not on the actual data submitted by the brand company. Thus, on its face, there is no basis whatsoever for the takings argument advanced by the brand-name companies.

¹⁷ 42 U.S.C. § 262(f).

¹⁸ FDA Citizen Petition filed by Genentech (April 8, 2004).

The implications of the brand industry's argument that the Constitution prohibits FDA from relying on its own decision to approve a brand product, and that Congress could not enact legislation directing or authorizing FDA to do so, are wide-ranging indeed. If accepted, these arguments would raise constitutional doubts about the status of a significant number of FDA and other regulatory agency programs. In certain regulatory programs, such as those covering food additives, medical devices, and over-the-counter drugs, FDA allows the entire industry to rely on an FDA approval based on test data submitted by regulated companies. Of course, companies are always subject to the limitations of patent laws.

Another argument put forth by the brand industry is that the science is unavailable to detect changes in protein structure between the brand product and the generic biopharmaceutical product. Yet, this contention ignores the fact that analytical scientific techniques and methods have rapidly advanced over the past decade. Comparative studies between the brand biopharmaceutical product and the generic biopharmaceutical have shown similarity in the primary, secondary, and tertiary structure of these products. It is possible today to demonstrate that the identity of these molecules correspond to the brand product. Biological activity has been shown to be consistent with international standards, including NIBSC (National Institute of Biological Standards) and WHO (World Health Organization), and published data from the brand products. Impurity profiles, both process and product-related, can be determined for generic biopharmaceuticals as well as for brand pharmaceuticals.

Generic biopharmaceuticals also are manufactured in the same manner as brand biopharmaceuticals. Changes to the manufacturing process for generic biopharmaceuticals are

addressed in the same manner as brand manufacturers in that comparability between the product prior and subsequent to such change is established. In short, generic firms approach safety, purity, potency, quality and manufacturing using the same scientific principles and standards as those relied upon by the brand sector.

Immunogenicity¹⁹ is another concern mentioned by brand manufacturers. We acknowledge that protein products are inherently immunogenic to some extent. FDA has put forth a risk-based approach for evaluation of immunogenicity. Although this approach was not created for a risk assessment of generic biopharmaceutical products, the elements of the approach can be extrapolated for this purpose. These elements include the knowledge that a manufacturer has of its product; the structural difference between the generic biopharmaceutical and the brand product and the ability of current technology to detect this structural change, if any; clinical relevance of bioassays (a measure of effectiveness), process and product impurity profiles, and the immunogenic potential of the protein. Such an approach would allow FDA to establish approval criteria regarding product safety on a product-by-product risk assessment basis.

¹⁹ A reaction to a substance that may range from reactions that cannot be detected to severe reactions.

Testing requirements also should vary depending on the complexity of the product. For example, a simple protein, such as interferon, should have a reduced pre-clinical and clinical program when compared to a glycosylated protein (proteins with sugar molecules), such as erythropoietin. Much data exist on the interferons: their protein structure, binding sites, and mechanism of action are well-known; the manufacturing process is understood and consistent; and, as these are redundant endogenous proteins, the immunogenicity profile is one in which adverse events are to be expected, but when they do occur, they are usually not life-threatening. Erythropoietin, on the other hand, is more complex due to glycosylation sites; and the immunogenicity profile for this unique endogenous protein is one where adverse events are rare, but serious. Accordingly, generic biopharmaceuticals should have a reduced pre-clinical and clinical program based on many factors, including those mentioned above. In fact, this approach has been publicly put forth by FDA as recently as 2003 for Human Growth Hormone and Insulin.²⁰

The Committee will want to carefully consider the appropriate design of a regulatory system that allows for generic biopharmaceuticals. In this regard, I would make several points.

First, the system needs to allow FDA the flexibility to tailor pre-clinical and clinical data requirements for biopharmaceutical products. The complexity of these products vary along a continuum, and FDA should have the authority to establish its requirements based on a scientific risk-benefit approach.

²⁰ FDA Presentation: Assessment of Comparability Using PK/PD (Jan. 7, 2003).

Second, Congress needs to direct FDA to impose only the regulatory requirements that are necessary to ensure similarity to the brand product and thus ensure that the affordable biopharmaceutical is safe and effective for its intended use. In 1984, Congress was concerned that FDA would impose burdensome requirements, and it included provisions in the Hatch-Waxman Act to address this concern. We urge Congress in drafting generic biopharmaceutical legislation to be mindful of the same concerns. And, Congress and FDA also should be mindful that ethical principles require that pre-clinical and clinical testing be required only where such tests are necessary to demonstrate safety and effectiveness.

Third, we urge Congress to direct FDA to play an active role in advising the generic biopharmaceutical companies about study design, data requirements and other issues, as it currently advises brand companies seeking authorization to market their products. Generic biopharmaceuticals will benefit consumers and healthcare providers and they will result in significant savings to federal government. It is in the public interest for FDA to offer constructive advice to companies seeking to develop these products, and to provide such advice early in the process and in a timely manner.

Finally, once Congress enacts legislation, we would urge it to monitor FDA's progress in implementing a generic biopharmaceutical program. Periodic reports to Congress may be appropriate. Unlike the approach that Congress imposed for chemical drugs, here it will be necessary that any legislation provide FDA with the flexibility to calibrate the regulatory requirements to the complexity of particular products. Unfortunately, this creates a risk of

unnecessary regulatory burdens and, for that reason, periodic Congressional oversight may be necessary.

In conclusion, Chairman Hatch and members of this Committee, we ask for your help. As a result of the 1984 Act, the generic drug industry now includes highly sophisticated and well-capitalized companies that are ready to enter this market. Scientific knowledge and technology have advanced to the stage where there are major biopharmaceutical products for which generics exist around the world. Yet, the lack of a clear and efficient regulatory pathway here at home hinders not only imminent product approvals, but also product research and development. Last fall and earlier this year, FDA was proceeding to issue a draft guidance, which would have begun the discussion about the appropriate regulatory requirements for generic biopharmaceuticals. Unfortunately, earlier this month, the agency announced that that guidance will be delayed until at least next fall. Meanwhile Genentech has suggested in its citizen petition that it will sue FDA even if the agency issues only a *draft* guidance.

In other words, Mr. Chairman, we are at a standstill. The case for generic biopharmaceuticals is every bit as strong as was the case for generic drugs in 1984. As we stated above, the use of biopharmaceuticals is expected to increase dramatically over the next decade. The introduction of generic versions of these important products would translate into a significant cost savings for the consumers who need them. Once the patents on these products have expired, it is essential that there be a clear regulatory pathway and that FDA regulatory requirements not be a barrier to competition.

This problem demands your attention. The generic industry stands ready to assist in any way we can, and we thank you for holding this hearing. I would be happy to answer any questions.