

# FOLLOW-ON BIOLOGICS

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## HEARING OF THE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS UNITED STATES SENATE ONE HUNDRED TENTH CONGRESS

FIRST SESSION

ON

EXAMINING FOOD AND DRUG ADMINISTRATION FOLLOW-ON BIOLOGICS, GENERALLY REFERRED TO AS A BIOTECHNOLOGY-DERIVED PROTEIN DRUG (OR BIOLOGIC) THAT IS COMPARABLE TO A NOVEL, PREVIOUSLY APPROVED BIOLOGIC AND THAT IS APPROVED WITH LESS SUPPORTING DATA THAN THE INNOVATOR BIOLOGIC

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MARCH 8, 2007

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THURSDAY, MARCH 8, 2007

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

The committee met, pursuant to notice, at 10 a.m., in Room SD-430, Dirksen Senate Office Building, Hon. Edward Kennedy, chairman of the committee, presiding.

Present: Senators Kennedy, Reed, Clinton, Brown, Enzi, Gregg, Alexander, Burr, Hatch, Allard, and Coburn.

### OPENING STATEMENT OF SENATOR KENNEDY

The CHAIRMAN. We'll come to order. Whoever that wonderful person is—Dr. Rossignol from Brussels. Thank you very much. We want to thank our distinguished witnesses for joining today's hearing on the important question of whether Congress should give FDA the authority to approve follow-on versions of biologic medicines.

We are in a remarkable period of discovery in the life sciences. Unprecedented advances are taking place and patients have already begun to see the benefits of this new era through new wonder drugs that can make the difference between life and death for patients afflicted with serious illnesses.

Patients with leukemia once faced a bleak future now have new hopes, thanks to an extraordinary new medicine that can slow or even halt the progression of the disease.

Until recently, a diagnosis of Gaucher's Disease meant a shorter life, full of disability and pain for the people it afflicted. Now, a remarkable breakthrough has produced drugs to treat this grave illness and extend life and reduce disability. Similarly, a drug to stimulate the production of new blood cells is helping patients counteract the severe anemia caused by chemotherapy or renal disease.

These miracle medicines, called biologics, are complex molecules whose healing power has been brought to patients by dynamic biotech companies. Such drugs were once a rarity in the medical arsenal but each day seems to bring new hope from new breakthrough biologics.

With this extraordinary progress comes a challenge to public policy. Due to the cost of developing and manufacturing new biologics, their price is often steep. They can cost patients tens or even hundreds of thousands of dollars a year, putting an extraordinary strain on the budgets of those who must pay the bills—patients, insurers and companies or government programs.

Congress has faced similar challenges before. In the early 1980's, the cost of prescription drugs was spiraling upward. In response, Congress enacted legislation that balanced the need to reduce costs for consumers through increased competition with the requirement to promote innovation. That legislation is known universally by the names of its sponsors, Senator Orrin Hatch and Representative Henry Waxman. Our committee is honored that Senator Hatch is helping guide our deliberations. Congress and the American people are indebted to his leadership on these important issues.

When the Hatch-Waxman law was enacted, Congress did not include biologics because at the time, such drugs were not providing the major innovations and advances in the biological sciences have brought over the past 20 years.

Now Congress must consider whether to authorize FDA to accept applications for follow-on versions of these path-breaking medicines. The stakes riding on the answer to this question are enormous, both for patients and our economy and the interest among our committee colleagues in this question is intense.

One of our colleagues, Senator Clinton, has a proposal to allow FDA to approve follow-on biologics. I look forward to hearing her views on this question and receiving the testimony of the legislation's cosponsor, Senator Schumer.

Many have recommended that the committee's legislation on drug safety and user fees should include a proposal to allow follow-on biologics. Today's hearings will help provide the information the committee needs to make the right decision on that important question.

Our committee should be guided by three basic principles. First, we must be led by the science. Acceptable legislation on follow-on biologics must not pre-judge science but should enable the FDA to make the best decisions based on the most complete science reasonably available.

Second, protecting patient safety is essential. Congress must make certain that any drug given to patients, whether a conventional drug, an innovative biologic or a follow-on-product is safe and effective.

Third, innovation must be valued and promoted. Just as it is essential to help patients afford the medicines of today, so too it is vital to provide incentives for the innovations that will bring the medical miracles of tomorrow.

I look forward to the recommendations and insights of our distinguished witnesses to provide guidance to our committee as we undertake these important deliberations.

Senator Enzi.

#### OPENING STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman, for holding this important hearing and beginning an important discussion regarding follow-on biologics. Part of the reason we need to have this hearing today is for us to understand the complex issues surrounding follow-on biologics. It's also a good opportunity to educate the public about the critical and complex nature of the issue.

Some will say that it is easy to think about providing a generic version of biologics, just like we provide generic versions of drugs.

However, that assumes that all drugs are just like biologics. They aren't. Biologics are very complex molecules modeled after key processes occurring daily within the human body. If a drug was a 3-bedroom, 2-bath starter home, a biologic would be a skyscraper. The size and complexity of the items are just that different.

Unlike drugs, which we can describe the structure with a high degree of precision, follow-on biologics elude similar scientific description.

So, if I was to try to build a skyscraper of a biologic without the blueprints, as any generic company would have to do to create a follow-on biologic, I would have to ensure that every copy was identical to the last or there could be fatal results. Thus, we must ensure that the science drives any sort of safety standard. One girder out of place could cause the entire structure to fall.

For all of their complexity, we can only imagine the potential of some of these potential miracle biologics, such as AIDs vaccine or cell therapy to cure diabetes. Today, some biologics are making it possible for thousands of Americans to live productive lives while others are changing the way we treat deadly diseases like cancer and infectious diseases. In the last 20 years, complex diseases such as multiple sclerosis and heart disease have been converted from virtual death sentences to manageable chronic conditions with the help of biologic drugs.

Over 20 years ago, Congress enacted legislation that provided a framework for the creation of generic drugs, generic versions of small molecules. In creating that initial framework, Senator Hatch and others crafted the watershed Hatch-Waxman legislation, which balanced innovation, safety, and incentives to create an abbreviated pathway for the approval for small molecule drugs. However, that legislation intentionally did not directly address follow-on biologics because they were too new and too complex to fit within that framework.

Now we're being asked to find an appropriate framework for the approval of follow-on biologics. In doing so, however, we must acknowledge the differences between drugs and biologics. In addition, any framework must acknowledge safety and preserve the fast pace of innovation.

I urge my colleagues to consider the ramifications of the legislation. If we get this wrong, then we face two potential undesirable outcomes—either new biologics will not be available to provide the next cure for life-threatening diseases or individuals die as we rush products to market without considering the safety implications.

We shouldn't rush a solution through Congress. We must take the time to fully consider other framework options, such as the European model for follow-on biologics. Any time we start legislating on complex scientific issues and don't know all the facts, we risk endangering lives.

Again, I thank the Chairman for holding this hearing and the witnesses for agreeing to participate. I look forward to learning a lot today. Thank you.

The CHAIRMAN. Thank you very much, Senator Enzi. I'm going to ask if Senator Clinton, prior to—she and Senator Schumer work very closely. She is a member of this committee and then perhaps if Senator Hatch, who's got a long—wants to say a word. We want

to keep the hearing moving along but Senator Clinton, obviously, has been a leader in the Nation on healthcare, very much devoted not only to the broad healthcare policy issues but also healthcare in regard to children and is interested in the quality issues. We work with her on the issues on information technology and this area of biologics as well and if she'd be good enough to say a word and then I'll introduce our first witness.

#### STATEMENT OF SENATOR CLINTON

Senator CLINTON. Thank you very much, Mr. Chairman and I want to thank you and Ranking Member Enzi for holding this hearing and I want to welcome my friend and colleague on this important issue, Senator Schumer. We have recently introduced the Waxman-Schumer-Clinton legislation to create a legal pathway for the approval of safe and effective follow-on biologics. And I would certainly underscore the concerns that Senator Enzi just enumerated. This obviously has to be done with great care and thoughtfulness but as I read the testimony last evening, I was struck by how far the discussion has come. There is finally acknowledgement that the science supports an abbreviated pathway for follow-on biologics, something many experts have asserted for years.

So, Mr. Chairman, we are finally at a place where we are debating how, not if and it will be up to this committee to decide when. Certainly the stakes are very high because the cost of biologics are a major and increasing proportion of our healthcare costs in America.

I'm not suggesting that this will be easy but we know from the previous efforts of this committee, certainly the Hatch-Waxman effort, where many of the same concerns and complaints were raised that if we work together and we do follow the science, we can devise appropriate legislation.

Our challenge is to sort through concerns with the Schumer-Clinton legislation, to separate those that are legitimate from those that are designed to erect barriers to the approval of safe and effective follow-on biologics.

So Mr. Chairman, this hearing starts that process. Certainly Senator Schumer and I believe we can cut costs, cut red tape, cut down barriers between people and safe, life-saving medicines and we are determined to work with everyone on both sides of the aisle to accomplish this critical goal.

So I look forward to the hearing and I thank the Chairman and Ranking Member for holding it.

The CHAIRMAN. Thank you very much, Senator Clinton. If it is agreeable with our colleagues, Senator Hatch has been a particular leader in this complex area that affects families to such a great degree and we appreciate both his presence here and his involvement on this issue. If he wanted to say a word, that would be great.

#### STATEMENT OF SENATOR HATCH

Senator HATCH. Thank you, Mr. Chairman and also Senator Enzi. I appreciate being here. Senator Schumer, we appreciate the work you're trying to do on this. This is a very important area. As



you know—as everybody knows, Hatch-Waxman, Waxman-Hatch—whatever you want to call it—

The CHAIRMAN. How do you call it?

[Laughter.]

Senator HATCH. I usually call it Hatch-Waxman. I noticed that Hillary calls it Waxman-Hatch but to make a long story short, it's been a very important bill because it's saved at least \$10 billion for consumers every year since 1984 and today, scientists tell me it is saving much more than \$10 billion a year.

But we have to do it right because follow-on biologics are a much more difficult thing to duplicate. And I think it is going to be very important—this hearing is a very important hearing to me and I think it is important to all of us. I personally appreciate the work that my friend, Henry Waxman and Senator Schumer and Senator Clinton have done. I don't quite agree with what they've done so I haven't agreed to sign on to that particular bill but I think they have brought everybody's attention to how important this really is.

I'm also very interested, Mr. Chairman, as you've made arrangements to talk about the European Union approach towards these issues. I think they have some very, very substantial ideas that we should certainly give every consideration to and we are giving consideration to and I, in particular, Mr. Chairman, and the Ranking Member, Senator Enzi, I am in particularly in your debt for taking this seriously and in meeting with you regularly, we're finding that I think we can maybe do some things here that are going to be very important in pushing biologic work forward, especially follow-on biologics. So I'm grateful to you, I'm grateful for this hearing and I look forward to hearing our witnesses.

The CHAIRMAN. Thank you very much. We welcome Senator Schumer, a long time champion of helping make breakthrough medicines more affordable for families, use the principle democratic sponsor of the Schumer-McCain legislation on generic drugs that was approved by this committee in the 107th Congress, today appears before the committee to speak on follow-on biologics. He and Senator Clinton and a bipartisan group of Senate colleagues have introduced legislation on this subject that is being studied closely by our committee. So we welcome him to our committee and thank him for taking the time to appear. We understand he's got pressing business, so we can submit questions if we have questions to him. Wouldn't you like to be able to question.

[Laughter.]

Senator SCHUMER. Why not? Everyone else does.

The CHAIRMAN. Everybody else does. Senator Schumer, we're delighted. This is very, very important and I know how interested you've been on this subject and we look forward to hearing from you.

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

Senator SCHUMER. Well, thank you, Mr. Chairman and I want to thank you for not only being gracious as always in allowing me to testify here today but for holding a hearing on this issue. I thank the whole committee for your work, just for my colleagues on the Republican side. Senator Clinton, I believe, was there but in one

of our caucuses, Senator Kennedy was outlining the work that is just ahead in this committee over the next month or two and it seemed like about three quarters of the agenda that America faces. So I very much appreciate the work that the committee has done under your and Senator Enzi's leadership, Mr. Chairman.

I also want to, of course, thank my colleague, Senator Clinton. This is another issue where we're working together and her intelligence and caring on so many issues in healthcare and across the spectrum once again, come through in this area and I thank you. And my good friend, particularly, Senator Hatch, who along with Senator Waxman in the Hatch-Waxman Act—I think it is probably one of the most important pieces of legislation passed in the last 25 years of the previous century for the good it has done. It has saved countless lives because people could afford drugs that they might not have been able to.

Anyway, just thinking back to Hatch-Waxman, if you look at the record, I was in the Congress then but not involved at all. I was a new Congress member but you look at all the objections that people raised when Senator Hatch and Congressman Waxman started their legislation. They were told the science wasn't there. They were told generic drugs would put the safety of consumers at risk and other issues. But their opponents were wrong and are wrong today when they make the same arguments about follow-on biologics.

As Senator Clinton has correctly outlined just a minute ago, the science is there now. We know how to do this. We can have discussions about when to do it and the way to do it but we know how to do it and we should. Biologics, of course, are a large and growing sector of the pharmaceutical market, provide treatments for devastating diseases, cancer and its complications. It provided some of the most important innovations in medicine in the last 100 years. But the innovations are only useful if there is competition in the market that lowers the price and makes them available to average folks, just as Hatch-Waxman did for chemical drugs.

Treating the patient with a biologic drug can cost \$100,000 a year, total cost to the nation, \$32 billion. If introducing competition in this market lowers the price of biologics even by only 10 to 25 percent, the savings are astronomical. Studies have estimated the potential savings for Waxman-Schumer-Clinton bill are tens of billions of dollars every year, similar to the savings that Hatch-Waxman now give us.

And obviously the science, as Senator Enzi has mentioned, is complicated. Biologics are not chemical drugs. It's much more complicated. We agree completely, we're not going to see all the savings at once but currently, the FDA's hands are tied. They don't have statutory authority to approve a lower-cost biologic product even if all the evidence is there to show the product is just as safe, pure and potent as the innovator's product.

So to get the process started, we believe we must provide the FDA with authority to act and this is the first step long overdue and it's what our bill does. Now there is a great deal of debate generated by our legislation. That's good. Certainly none of us wants a new law that doesn't adequately protect either the consumer or the health of the patient and we don't want a law that stifles inno-

vation by making biologic drugs unprofitable. That would make no sense whatsoever. So there is a lot of balancing that has to be done here.

Now my time is brief so I just want to make two points, one on the EU system and the other on patents. I want to welcome Mr. Rossignol from the EU to this hearing because the EU has already moved forward on approving what they refer to as biosimilars and I think their experience is valuable but I would urge the committee to consider this experience carefully. There may be valuable lessons to be learned from a system that is already in place but we must fully understand how that model might work in our own market. First, we should understand how the EU system came to be and how it worked in practice. As it stands today, the EU has a highly regulated process in place that has arguably, at least and unnecessarily burdensome to competitors and here's the interesting fact. It has only resulted in two approvals to date. This process was not established by legislation that was passed by the European equivalent of Congress, however. The statute that created a pathway to biosimilars in the EU was written in broad language, which gave Europe's equivalent of the FDA discretion to flesh out the details. So when I think about the EU model, I agree we should pass legislation that would give the FDA the discretion but why would the United States want to deprive the FDA of the ability to draft its own regulations and force them to swallow a complex set of regulations that has been created by another government, a system of government that has a different way than ours. It has price controls and the EU's generic market is not as robust as the market that Senator Hatch and Congressman Waxman created.

Finally, on patents—just for a moment. As I mentioned earlier, we have to strike a balance between rewarding innovation and increasing access to lower cost pharmaceuticals. Many people inside this room, outside this room have ideas about how that would happen. The only thing I want to point out before I conclude is that when Hatch-Waxman was passed, it struck a bit of balance between the innovators and the generics for traditional chemical changes but created an imbalance for biologics. It gave the biologic manufacturers the same 5-year patent extensions that chemical manufacturers received and gave them the same access to 7 years of exclusivity under the Orphan Drug Act but did not set up an abbreviated pathway for the approval of biologic competitors.

Therefore, I would argue that Waxman-Schumer-Clinton is not imbalanced but rather is restoring a balance in a sector of the pharmaceutical market that has never faced competition. So I know that some colleagues think we're moving too quickly. I think those of us on our bill think we haven't moved quickly enough. We've waited years for the FDA to issue White Paper or guidelines. The science is there. The groundwork has been laid and of course, every day we deny the FDA this authority, it means more delay in savings on vital medicines and again, I thank the Chairman and would be happy to answer any questions in writing.

[The prepared statement of Senator Schumer follows:]

## PREPARED STATEMENT OF SENATOR SCHUMER

Thank you, Mr. Chairman, for allowing me to testify before the committee today, and for holding a hearing on this very important issue.

I am the sponsor, along with my friend Senator Clinton here in this committee and with Congressman Waxman in the House, of the Access to Life-Saving Medicine Act, which would establish a pathway for competition in the market for biologic products.

As I sit here today, I'm reminded of the laudable work of my colleague Senator Hatch here and of Congressman Waxman to establish the first pathway for competition in the chemical drug market over 20 years ago.

Back then, they were told that the science wasn't there. Back then, they were told that generic drugs would put the safety of consumers at risk. But their opponents were wrong then, and are still wrong today when they make the same arguments about follow-on biologics.

Mr. Chairman, biologics are a large and growing sector of the pharmaceutical market. They provide treatments for devastating diseases such as cancer and its complications, and have provided some of the most important innovations in medicine in the last 100 years. But these innovations are only useful to the public if there is competition in the market that lowers the price and makes the drugs available to everyday people.

Treating a patient with a biologic drug can cost \$100,000 per year, at a total cost to the Nation of \$32 billion per year. Even if introducing competition to this market only lowers prices of biologic drugs by 10 percent to 25 percent, the savings on products this expensive will still be astronomical. Studies have estimated the potential savings of the Waxman-Schumer-Clinton bill at tens of billions of dollars every year.

We know that this field of science is complicated. We know that we won't see the savings all at once. But currently, FDA's hands are tied, and they have no statutory authority to approve a lower-cost biologic product even if all the evidence is there to show that the product is just as safe, pure, and potent as the innovator's product. To get this process started, we must provide FDA with the authority to act, and this first step is long overdue.

That's exactly what our bill does. The Access to Life-Saving Medicine Act gives FDA the authority to approve follow-on biologics and the discretion to determine what kind of information is needed to ensure that they are safe and effective.

I understand that a great deal of debate has been generated by this piece of legislation, and I welcome it. Certainly none of us wants a new law that does not adequately protect the consumer, or a law that stifles innovation by making biologic drugs unprofitable for the brand industry.

So as we move forward with this debate, I would like to make two points, one on the EU system, and the other on patents.

I'd like to welcome Mr. Rossignol from the European Union to this hearing, and since the EU has already moved forward on approving what they refer to as "biosimilars," I think their experience is valuable.

But I would urge the committee to consider this experience carefully. There may be valuable lessons to be learned from a system that is already in place, but we must fully understand how that model might work in our own market.

As it stands today, the EU has a highly-regulated process in place that has arguably been unnecessarily burdensome to competitors and has only resulted in two approvals to date. This process was not established by the legislation that was passed by the European equivalent of Congress, however. The statute that created a pathway to biosimilars in the EU was written in broad language which gave Europe's equivalent of the FDA discretion to flesh out the details.

So when we think about this model, I agree that we should pass legislation that would give the FDA the discretion to establish a scientific approval process as they see fit. But why would the United States of America deprive the FDA of the ability to draft its own regulations, and force them to swallow a complex set of regulations that has been created by another system of government? A system of government, I might add, that has price controls and a generic drug market that is not as robust as our own.

And finally, I'll spend a moment on patents. As I mentioned earlier, we need to strike a balance between rewarding innovation and increasing access to lower-cost pharmaceuticals.

I'm sure many people in and out of this room have ideas on how they'd like that to happen.

But let me just point out that in 1984, when the Hatch-Waxman law was passed, it struck a balance between the innovators and the generics for traditional chemical drugs, but also created an imbalance for biologic drugs.

It gave biologic manufacturers the same 5-year patent extension that chemical manufacturers received, and also gave them the same access to 7 years of exclusivity under the Orphan Drug Act, but did not set up an abbreviated pathway for approval of biologic competitors.

Therefore, I would argue that the Waxman-Schumer-Clinton bill is not imbalanced, but rather is restoring balance in a sector of the pharmaceutical market that has never faced competition.

I know that some of my colleagues are concerned that we are moving too quickly. I am concerned that we have not moved quickly enough. We have already waited for years for the FDA to issue a white paper on follow-on biologics. The science is there, the groundwork has been laid, and every day that we deny the FDA this authority means more delay in savings on vital medicines for consumers.

Thank you, Mr. Chairman.

The CHAIRMAN. Seriously, we thank you for a very thoughtful presentation on a complex issue but one of enormous importance to people. We thank you very much.

Senator SCHUMER. Thank you.

The CHAIRMAN. We'll have a panel now and ask Mr. Sid Banwart, Vice President of Human Services for Caterpillar and is responsible for the compensation benefit for Caterpillar's 95,000 employees worldwide. Mr. Banwart joined Caterpillar in 1968, served in numerous positions throughout the organization. Mr.

Banwart also chairs a National Coalition for the Human Resource Policy Association to create a new, transparent model for purchasing pharmaceutical drugs.

Dr. Nicolas Rossignol is a Senior Administrator of the European Commission Unit responsible for the implementation of the EU pharmaceutical legislation. He is in charge of all issues related to the biological medicines and since 2003, has been responsible for the implementation of an EU regulatory framework on follow-on biologics. He also represents the European Commission in technical discussions on follow-on biologics held by the World Health Organization. We thank you very much for joining us from Brussels this morning.

Dr. Jay Siegel is a Group President of Research and Development at Johnson and Johnson Pharmaceutical. He is responsible for the oversight of research and development in biotechnology, immunology and oncology. Prior to joining J&J in 2003, Dr. Siegel was at FDA Center for Biologics, the evaluation of research for 20 years. Dr. Siegel also has a special connection to the Kennedy Office. He is married to Dr. Mona Safroty, who worked on my health staff for many, many, many years and is now serving with the station on the faculty of the George Washington University of Public Health. So we welcome Dr. Siegel once again to our committee room.

Dr. Ajaz Hussain is Vice President and Global Head of Biopharmaceutical Development at Novartis with a responsibility for the development of follow-on biologics. Before joining Novartis, Dr. Hussain served as the Deputy Director of the Office of Pharmaceutical Science in FDA Center for drug evaluation and research, where he had oversight responsibility for the development of science-based regulatory policies. I'm very grateful to you.

So Mr. Banwart, we'd be glad if you'd be good enough to start off. We welcome the opportunity—we thank all of you for joining with us.

**STATEMENT OF SID BANWART, VICE PRESIDENT OF HUMAN SERVICES, CATERPILLAR, PEORIA, ILLINOIS**

Mr. BANWART. Thank you, Chairman Kennedy, Senator Enzi and other members of the committee. I'm pleased to present testimony on behalf of Caterpillar regarding the need to establish an abbreviated science-based regulatory pathway for approval of biogeneric products within the FDA.

We commend you for your swift action in holding this important hearing to begin the process to apply balance and competition in the biotechnology market. My name is Sid Banwart and I'm the Vice President at Caterpillar responsible for the Global Human Services Division, which does include compensation and benefits.

As the world's largest manufacturer of construction and mining equipment, engines and related services, Caterpillar has 95,000 employees worldwide, is a major U.S. manufacturer and is a leading exporter, with some \$10.5 billion worth of U.S. built products shipped around the world in 2006. Caterpillar's ability to maintain our position of market leadership depends on our success in attracting and retaining top talent and we use our benefits package

to recruit the best and brightest from some of the top schools in the country, to assure the future of Team Caterpillar.

We are continuing to take positive measures, many positive measures to keep our employees and retirees healthy while managing cost. Last year alone, we spent more than \$600 million in the United States for comprehensive healthcare benefits for Team Caterpillar. We strongly encourage a vigorous and competitive prescription drug market, one in which innovation leads to new life-saving medicines. We recognize that one important element of innovation is patent protection but at the end of the patent term, we welcome competition in the marketplace.

Currently, there is no opportunity for competition once a patent has expired on brand biotech drugs because the FDA does not have clear authority to approve biogeneric products and—let me be clear here—by biogeneric, I mean a lower cost alternative, whether the industry parlances comparable or interchangeable or therapeutic equivalent or generic, we want an abbreviated process that results in biogenerics.

So I appear before you today to urge this committee to find a bipartisan solution to create an appropriate regulatory route for FDA review of biogenerics. We believe any solution should grant the FDA authority to use its discretion and scientific expertise to evaluate interchangeable and comparable biogeneric products while ensuring patient safety. One of the most important healthcare laws enacted over the past 30 years was the Hatch-Waxman Act. This law saves patients, employees and payers billions of dollars every year and we thank you, Senator Hatch, for your leadership.

Now it's time for an important next step, to create a similar process to spur competition within the biotechnology market. In 2006, Caterpillar's prescription drug costs were in excess of \$151 million, accounting for more than 25 percent of our total healthcare spending and while biologics currently account only for 3 percent of the total drugs utilized, they account for 12 percent in terms of the dollars spent and these biologics have increased in cost 45 percent just since 2004. This is our single fastest growing category of health cost and the trend is simply not sustainable.

Caterpillar encourages the committee to consider five key principles, which I've expanded upon in my written testimony, as you begin to develop legislation. Protect and promote fair and open competition. Two, provide a definitive pathway for the approval of biogenerics. Three, encourage consistent and uniform terminology. Four and this is very important in my mind, increase the resources for the FDA. Five, include new legal authority for a biogeneric pathway in your must-pass legislation this year.

In conclusion, I'm pleased that the Senate HELP Committee is considering issues like biogenerics that can make a positive impact on our health care system and would provide public and private benefits in terms of additional certainty in forecasting for healthcare spending and as already has been said, overall cost savings. So thank you to the members of the committee who have taken an active interest in understanding the important role of the FDA to use its scientific judgment to approve biogeneric products.

Chairman Kennedy, Senator Enzi, we appreciate your leadership and that of others on the committee who have been out front on

this issue. More Americans should be given access to these important innovations and we encourage you to support a marketplace that has fair and open competition. Thank you for this opportunity to testify today.

[The prepared statement of Mr. Banwart follows:]

#### PREPARED STATEMENT OF SID BANWART

##### INTRODUCTION

Chairman Kennedy, Senator Enzi and other members of the committee, I am pleased to present testimony on behalf of Caterpillar regarding the need to establish an abbreviated, science-based regulatory pathway for the approval of biogeneric products within the Food and Drug Administration. We commend you for your swift action in holding this important hearing to begin the process, launched by the bipartisan efforts of Senators Schumer, Clinton, Stabenow, Leahy, Vitter, and Collins, to apply balance and competition within the biotechnology market.

##### CATERPILLAR BACKGROUND

My name is Sid Banwart. I'm vice president at Caterpillar where I have responsibility for the company's Human Services Division, which includes Compensation and Benefits.

As the world's leading manufacturer of construction and mining equipment, diesel, natural gas and turbine engines, and related services, Caterpillar employs nearly 95,000 employees worldwide, is a major U.S. manufacturer and leading exporter with some \$10.5 billion of U.S.-sourced product shipped around the world in 2006.

Caterpillar is able to be a leader in the global marketplace utilizing its strong U.S. manufacturing base because we make competitive products that are known for their quality and durability. But our ability to remain a market leader depends on our success in attracting and retaining top talent. We use our benefits package to recruit the best and brightest from some of the top schools in the country and consider those new grads to be the future of Team Caterpillar.

##### HEALTH CARE STORY

To ensure our company is well positioned in that future, we are continuing to take aggressive measures to keep our employees and retirees healthy, while managing cost. As you know, the escalation of health care costs is a top concern for U.S. business executives, and we at Caterpillar are no exception. Last year alone, we spent more than \$600 million in the United States for comprehensive medical, dental, vision, and prescription benefits.

To manage our costs, we've taken action on both the wellness and cost sides of the equation. On the wellness front, Caterpillar has in place an award winning health promotion program, disease management systems, and our Work.Life.Solutions program to promote a balanced lifestyle. On the cost side, we've established preferred hospital groups, physician networks and a pharmacy benefit management arrangement to ensure the best possible rates and enhanced transparency in pricing.

##### VIEW ON PRESCRIPTION DRUG MARKETPLACE

Caterpillar strongly supports a vigorous and competitive prescription drug market, one in which innovation leads to new life-saving medicines. Currently there is no opportunity for competition in the marketplace once a patent has expired on brand biotech drug products because the Food and Drug Administration (FDA) does not have clear authority to approve biogeneric products. I appear before you today to urge this committee to find a bipartisan solution to create an appropriate regulatory route for FDA review of biogenerics. We believe the solution should grant the FDA the authority to use its discretion and scientific expertise to evaluate interchangeable and comparable biogeneric products while ensuring patient safety.

##### HATCH-WAXMAN LAW

One of the most important health care laws enacted over the past 30 years was the "Drug Price Competition and Patent Term Restoration Act of 1984," commonly known as the "Hatch-Waxman" law. As Senator Hatch knows so well, this landmark legislation broke important new ground in granting FDA the authority to approve generic versions of prescription products. Hatch-Waxman also gave FDA express authority to provide an abbreviated approval process for those products deemed equiv-



alent to the prior approved product. It is estimated that this law saves patients and payers billions per year—and we thank you, Senator Hatch, for your leadership in this important area, as well as your recent commitment to work to pass legislation this year to spur competition within the biotechnology market.

CONSUMERS AND PURCHASERS WILL BENEFIT WITH GREATER INNOVATION  
AND GREATER COMPETITION

Total spending on prescription drugs in 2006 is estimated at \$213.7 billion and rising to \$497.5 billion by 2016.<sup>1</sup> The use of biopharmaceuticals is increasing at almost twice the rate of traditional medicines—accounting last year for approximately \$30 billion in U.S. sales and 12 percent of total pharmaceutical usage.<sup>2</sup> These medicines can and do improve the lives of millions of patients—but without generic versions, the costs may keep needed treatments out of the hands of consumers.

Caterpillar is focused on drug issues because we expect prescription drug expenses to be among the most significant health care cost drivers for our company in the years ahead due to an aging workforce and increased rates of utilization. For 2006, Caterpillar's prescription drug cost were in excess of \$151 million, accounting for more than 25 percent of our health care total spent. For our company, biologics currently account for 2.9 percent of the total drugs utilized but account for 12 percent in terms of spending. Most concerning is the financial trend Caterpillar has documented with biologic products . . . costs have increased 45 percent since 2004. This is our single fastest growing category of health cost, and the trend is simply not sustainable.

CERTAINTY

Caterpillar, like other U.S. manufacturers, is very concerned about the implications of our health care expenses. For business planning purposes, it is critical for us to have certainty when forecasting spending . . . be it for commodities such as steel or for health care benefits like prescription drugs. Currently there is no certainty in our pharmaceutical spending because we do not know when or if there will be lower cost alternatives for biopharmaceuticals. Many of the biopharmaceuticals on the market today are “off-patent” and more than \$10 billion worth of biopharmaceuticals are expected to come off patent by 2010.<sup>3</sup> When exploring avenues to introduce competition into the marketplace, I ask Congress to clearly outline a reasonable process for early resolution of patent disputes to avoid any unintended loopholes and ensure certainty for the biogeneric marketplace.

GUIDING PRINCIPLES FOR BIPARTISAN LEGISLATION

Caterpillar encourages the committee to consider five key principles as you begin to consider legislation:

**1. Protect and promote fair and open competition.** As innovators, we respect and understand the development of innovation and need for patent protections. However, once a patent expires or is successfully challenged, biogeneric competition should be able to enter the market.

**2. Provide a definitive pathway for the approval of biogenics.** We believe there must be certainty in both timing and method of the biogeneric approval process. FDA needs the authority—to approve both comparable and interchangeable biogeneric products. Congressional deference to the FDA's expert scientific judgment is appropriate. In addition, any action should permit prescribers to substitute one biologic for another when appropriate.

**3. Encourage consistent and uniform terminology.** Whether the terms are “comparable,” “interchangeable,” “therapeutic equivalent,” or “generic”—we want an abbreviated process that results in a “biogeneric,” meaning a lower cost alternative to biologic pharmaceuticals.

**4. Increase resources for the Food and Drug Administration.** In order to adequately assume these new responsibilities, the FDA will need adequate resources. We support additional resources for FDA to secure more staff to ensure the timely review of biogeneric applications and the safety of biogenics for consumers.

<sup>1</sup>Poissal, J.A., et al., “Health Spending Projections Through 2016: Modest Changes Obscure Part D's Impact,” *Health Affairs* 26, no. 2 (2007) Exhibit 6.

<sup>2</sup>*MedAdNews*, November 2006.

<sup>3</sup>Engel & Novitt, LLP, “Potential Savings That Might Be Realized by the Medicare Program From Enactment of Legislation Such as The *Access to Life-Savings Medicine Act* (H.R. 6257/S. 4016) That Establishes A New CBLA Pathway For Follow-On Biologics. Table 4a, January 2, 2007.

**5. Include the new legal authority for a biogeneric pathway in must-pass legislation this year.** We encourage Congress to move quickly to establish a regulatory pathway for the approval of biogenics. We are confident that this hearing will affirm that the science for comparable and interchangeable products has arrived. Once the FDA has the discretionary authority to begin this process, it will drive innovation that will assist in the identification of similar and substitutable methods for these off-patent products. Each day that passes without biogenics is another day of limited options. No payer, whether individual or employer, public or private, can afford unlimited monopoly pricing. Caterpillar, therefore, is encouraged to hear reports that members are committed to including a workable pathway into the prescription drug reauthorization legislation—called PDUFA—and strongly supports you in this endeavor.

#### CONCLUSION

In conclusion, I'm pleased that the Senate HELP Committee is considering issues like biogenics that can make a positive impact on our health care system. Thank you to all the members of this committee who have taken an active interest in understanding the important role of the FDA to use its scientific judgment to approve biogeneric products. Chairman Kennedy and Senator Enzi, I appreciate your leadership and also that of others on the committee who understand and have taken leadership on these issues. A bipartisan bill that empowers the FDA to use the best science to encourage innovation and biogeneric competition should be passed this year. More Americans should be given access to these important innovations—we encourage you to support a marketplace that has fair and open competition. Thank you for this opportunity to testify today.

The CHAIRMAN. Thank you very much.  
Dr. Siegel.

#### **STATEMENT OF JAY P. SIEGEL, M.D., GROUP PRESIDENT, BIOTECHNOLOGY, IMMUNOLOGY AND ONCOLOGY, RESEARCH AND DEVELOPMENT, JOHNSON & JOHNSON, RADNOR, PENNSYLVANIA**

Dr. SIEGEL. Good morning, Mr. Chairman and members of the committee. Thank you for your introduction. I'll skip over my employment but I would like to note in the context of today's hearing that in my 20 years in the public health service, I was responsible, entirely over that 20 years for regulation of biologics, over the final 7 years for the review and approval of all biological therapeutics and led the review and approval of about 50 such products and particularly relevant to today's hearing, played an essential role in setting scientific standards for ensuring the comparability of biological products after manufacturing changes. I am speaking on behalf of Johnson & Johnson and I thank you for the opportunity to be here today.

My company and I appreciate and share the concern shown by Senators Clinton and Schumer and others here for expanding access to biologic therapies. I also appreciate the concern this committee and other members have repeatedly demonstrated for protection of patient safety and welfare.

A concern we all share and that must guide us as we develop a statutory pathway for follow-on biologics. To that end, I will discuss several science-based principles that are critically important to address in any regulatory paradigm for follow-on biologics.

First, there will always be a need for appropriate pre-marketing testing in humans to ensure that a follow-on biologic is safe and effective. In contrast to typical non-biologic drugs, biologics are often 100 to 1,000 fold larger or more complex. They are produced

by living cells in tissues and organisms and they are highly susceptible to changes.

As is detailed in my written testimony, recent history is replete with examples of how seemingly minor manufacturing changes for biologics have led to inadvertent changes in the biologic product. Due to the complexity of biologics, these changes often are not detectable by laboratory testing but they can present significant risks for patients.

The production of follow-on biologics will necessarily involve substantial changes in the manufacturing process and laboratory testing of follow-on biologics will be even more limited in its ability to detect resultant product differences because the manufacturers have incomplete access to knowledge and materials necessary for optimal testing.

To ensure safety and efficacy, testing in humans will be needed. The types and extent of clinical testing required for follow-on biologics' approval will need to be determined on a case by case basis, considering factors about the product, its laboratory testing and its potential effects in patients.

The second principle is this: there need not and should not be allowance for determinations of comparability for products that are so different in structure that they should be considered different products entirely. While generic drugs have identical active ingredients, it is essentially impossible to make a follow-on biologic with an identical active ingredient. Thus, if we are to move forward with an abbreviated biologics application for follow-on biologics, they need to be based on biologics being highly similar rather than identical.

But there is no need nor scientific basis to allow abbreviated applications despite differences so substantial they could readily be avoided by the manufacturer and that they present the significant likelihood of differences in the safety and efficacy of the biologic.

Third, a follow-on biologic should not be considered interchangeable with its reference product. Within the limitations of science today and in the foreseeable future, there is no realistic potential for scientifically valid determination of interchangeability. Follow-on biologics can be shown to be similar but never identical to an innovator biologic. Application of interchangeability status to a follow-on could lead to inappropriate assumptions of sameness and substitution of one for the other. Such substitution could not only have potentially serious health consequences but could seriously impair the ability of post-marketing surveillance systems to detect new safety problems and to determine which biologic was responsible. Indeed, follow-on biologics policy should discourage inadvertent substitution.

Fourth, FDA must be empowered to require post-marketing clinical studies and post-marketing safety surveillance needed to ensure safety.

Fifth, any proposed pathway for follow-on biologics should not constrain the FDA's ability to request data and studies in support of sound scientific decisions.

In conclusion, it is my hope and that of Johnson & Johnson that a scientifically-based public process will provide a framework and pathway for follow-on biologics in the United States, a pathway

which reflects an overriding concern for patient safety and well being. It is also critical that this pathway provides appropriate incentives for innovation so that the promise of new and innovative biological therapies can continue to be realized for patients for generations to come.

I thank you again for the opportunity to speak here today and look forward to answering questions you may have.

[The prepared statement of Dr. Siegel follows:]

PREPARED STATEMENT OF JAY P. SIEGEL, M.D.

Good morning, Mr. Chairman and members of the committee. My name is Dr. Jay Siegel, and I am pleased to come before you today to offer a scientific perspective on the issues relevant to any proposed framework for the abbreviated approval of follow-on biologics. I will provide examples from my experience to illustrate the significance of these issues. I hope you will find my contribution to this discussion constructive and useful as you seek out a sound, science-based path forward for follow-on biologics. I particularly appreciate the concern shown by Senators Clinton and Schumer, the sponsors of S. 623, the Access to Life Saving Medicine Act, for patient access to biologic therapies. It is a concern that I share—as does my company, Johnson & Johnson.

By way of introduction, I studied biology at the California Institute of Technology and received my medical degree from Stanford University. My post-doctoral training was in Internal Medicine at the University of California San Francisco and in Infectious Diseases and Immunology at Stanford. As a scientist with specific expertise in the fields of biotechnology, immunology, and clinical trial design, I have dedicated much of my life and career to public health, working 20 years regulating biologics at the Food and Drug Administration (FDA), including as the founding Director of the Division of Clinical Trial Design and Analysis and then as Director of the Office of Therapeutics Research and Review within the Center for Biologics Evaluation and Research (CBER, 1996–2002).

In this role, I supervised the medical and scientific team responsible for the evaluation and approval of all biological therapeutics, including monoclonal antibodies, cytokines, growth factors, enzymes, cellular and gene therapies. I have led the review and approval of more than 50 new therapies. Particularly relevant to today's hearing, I also led efforts to develop FDA policy regarding scientific standards for demonstrating the comparability of biological products after a manufacturing change.

In the course of ensuring appropriate regulation of biologics, my associates at FDA and I worked closely with Members of Congress and testified before committees such as this one to communicate the complexities of biological therapeutics, their promise, and, at all times, our concern that they be as safe as possible for patients. I know that patient safety is a concern that we share and that it will be the guiding concern for you as you develop a statutory pathway for follow-on biologics.

Presently, I am Group President of Research and Development for Biotechnology, Immunology, and Oncology for the Johnson & Johnson family of companies, one of the world's largest producers of biotechnology-derived biologics, and today I am speaking on behalf of Johnson & Johnson. Having devoted decades of my life as a regulator and scientist working on biologics, I sincerely hope my experience will help you in the task ahead.

While legislation on follow-on biologics has the potential to improve access to life-saving medicines, that legislation should be well-founded in science and ensure that the lifesaving medicines to which access is provided are no less life-saving or safe than medicines already on the market. I believe that through the proper process, those critical ends can be met.

There are many important examples from the recent past that should give rise to caution about the possibility that follow-on biologics could have important differences from their reference products. This concern results from the complexity of biologic products and the inability to fully characterize them. Experience has taught us that there is significant likelihood that differences in a product will result when it is made by a different manufacturer; that such differences cannot always be detected except through clinical testing; and that such differences can have potentially serious ramifications for the health and safety of the patients that we all serve.

I would now like to focus my remarks on five principles that I feel are critical to address carefully in any follow-on biologics legislation:

- First, there will always be a need for appropriate pre-marketing clinical data to ensure that a follow-on biologic is safe and effective.
- Second, there cannot be allowance for determinations of “comparability” for products that are so different in structure that they should be considered different products entirely.
- Third, a follow-on biologic product should not be considered interchangeable with its reference product.
- Fourth, FDA must be empowered to require post-marketing clinical studies and post-marketing safety surveillance to ensure safety.
- Fifth, there should be no constraints placed on the FDA for ensuring the safety of follow-on products.

I would now like to share with you my scientific perspectives on these key areas in more detail.

#### 1. ANY PATHWAY FOR FOLLOW-ON BIOLOGICS SHOULD REQUIRE PRE-MARKET CLINICAL DATA FOR DEMONSTRATION OF SAFETY AND EFFICACY

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

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

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

Minor differences in production conditions in these living “factories” can lead to important differences in their product. To a far greater extent than small molecules, biologics frequently can bind to themselves to form pairs or aggregates, can change their shape over time or with minor changes in conditions, and can interact with materials in their containers and packaging. They are relatively unstable and are sensitive to how they are handled, processed and stored as they have the ability to assume many forms and variants. They are typically not homogeneous in chemical structure; rather, they are a large family of molecules with related, but not identical, structures. They cannot be fully characterized, so not only are differences common, they can be extremely difficult to detect, and their effects on the product’s safety and efficacy are extremely difficult to predict.

As a result, the regulation of biologics is strongly based upon strict control of the manufacturing process to minimize the likelihood of changes to safety and efficacy. And additional clinical testing is often required when substantial changes to the manufacturing process occur.

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

When a biologics manufacturer makes a substantial change to its process (e.g., new cell line), given the incomplete ability of laboratory testing to identify or predict differences, FDA requires substantial testing in humans (clinical testing) to validate the comparability of the product. This was the case when I was at FDA and remains the case now. And that clinical testing not infrequently reveals differences (see some of the examples below). The manufacture of a follow-on will by definition involve very substantial changes—a new cell line, a new facility, and, to varying extents, a new process—raising the relatively high likelihood of clinically important differences.

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

in the final product. Manufacturers of follow-on biologics will not have these materials for testing and will only have access to final, marketed reference product.

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

Thus, a manufacturer of a follow-on biologic will face significantly more limitations in demonstrating comparability than a manufacturer modifying its own process. At Centocor, a Johnson & Johnson company that develops biological therapies, when we make changes that might affect the clinical effects of a product, while we do extensive laboratory testing, we nonetheless also face an appropriate requirement for clinical studies to ensure safety and efficacy. How can we accept a lesser standard of evidence from the manufacturers of follow-on biologics, who face even greater limitations in laboratory testing, without significant concerns for safety?

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

#### *Examples*

There are many examples of how seemingly minor changes in a biologic’s manufacturing process have resulted in significant changes in the product. And while these changes sometimes are undetectable in laboratory testing or are “minor” enough to qualify under S. 623 as preserving “highly similar principal molecular features,” they can often trigger clinically important changes in the product’s safety and efficacy—changes that, at times, can be detected only through clinical testing.

I would like to use some specific examples to ensure that this committee’s members understand that my concerns are not theoretical or alarmist in nature, but are in fact very real issues that need to be considered.

In recent years, at Johnson & Johnson, we changed the cell line used to make an experimental biologic called CNT095. By physical and laboratory testing, the product made by the new cell line looked quite similar to the old product, so it would have passed a comparability determination were clinical testing not needed. But clinical testing revealed that the new product had different pharmacokinetics: that is, the drug levels in the body over time were different from those seen when the old cell line was used. This sort of change in pharmacokinetics, revealed only in clinical studies, was an extremely common occurrence observed during my time at the FDA.

In my experience at the FDA, even seemingly innocuous manufacturing changes for a biologic product often led to significant differences—sometimes detected only through clinical testing. In another example, a manufacturer opened a new facility in Japan to treat patients in Japan. The process used at the new facility was made as similar as possible to that of the pre-existing facility. Laboratory testing of the physical and chemical properties and bioassays showed no differences between products made at the new and pre-existing facilities. But in clinical testing, blood levels of the biologic were 40 percent lower in patients taking the product manufactured in the new facility versus the old. Although it was initially suspected that this reflected a difference in the patient population, further studies indicated the difference was indeed in the drug itself.

Sometimes, changes that seem not only innocuous but beneficial can create problems. Proleukin is a biologic for treatment of cancer that contains a detergent used in manufacturing. Prior to licensure, the manufacturer lowered the detergent levels in an attempt to make the product more pure. Product made by this new process passed routine testing. Highly specialized additional testing later found that the new product had increased microscopic clumping. This microscopic clumping re-

sulted in rapid clearance of the drug from the circulation. In yet other examples, a change as seemingly minor as placing a product in a pre-filled syringe instead of a vial has led to clinically meaningful changes to several biologic products: One interacted with silicone in the syringe, one interacted with trace metals in the needle, and, as discussed below, one interacted with the rubber stopper on the syringe plunger.

#### *Immunogenicity*

Special attention should be given to the problem of immunogenicity: i.e., the ability of most or all biologic products to stimulate an immune system response in the body, prompting the formation of antibodies. Immunogenicity is particularly important in the context of manufacturing changes for a biologics because (1) product differences that are difficult or impossible to detect can lead to changes in immunogenicity; (2) changes in immunogenicity can impact on safety and efficacy in many ways and (3) immunogenicity can be assessed only through clinical testing. The immune system evolved to distinguish foreign proteins (e.g., bacteria, viruses, proteins from other people) from its own proteins as a means of survival. This means that our immune systems can be exquisitely sensitive to differences in proteins.

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

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

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

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

Avonex® is an interferon beta product used to treat multiple sclerosis. After clinical testing proved that interferon beta was safe and effective for this use, the manufacturer needed to develop a new cell line to make the biologic and manufactured it in a new facility. While the Agency would normally be quite reluctant to permit a change in cell lines at this late stage of development, there was a public health need for this treatment which had been shown in clinical studies to be effective in treating multiple sclerosis. However, the original cell line used to make the drug for clinical studies was no longer available to the manufacturer and it was necessary to use another cell line in order to bring this product to patients.

Only after a couple of years of work using the new cell line was the manufacturer able to make an interferon beta product, Avonex, that appeared highly similar to the material used in the clinical trials that showed safety and efficacy. While the manufacturer was not required to repeat multi-year clinical testing, substantial clinical study was done before approval. Thereafter, post-marketing clinical experience showed that Avonex did indeed have clinically relevant differences from the earlier, clinically tested material. Fortunately for all, Avonex differed in that it had *less* immunogenicity. This example contributed to heightened awareness of the potential for manufacturing changes to lead to immunogenicity changes and of the importance of immunogenicity testing after many types of manufacturing changes.

The case of EPREX®, a biologic product sold in Europe by Johnson & Johnson companies, illustrates how even a seemingly minor change can increase a product's immunogenicity and cause harm to patients. In 1998, our company changed the stabilizer in its EPREX formulation at the request of European authorities because of concern in Europe that the human serum albumin stabilizer could theoretically

transmit Mad Cow Disease. The switch from the old stabilizer to another well-established one seemed simple enough and relatively benign. Indeed, it was intended to improve the safety profile. It was applied to a variety of product presentations, including single-use vials and pre-filled syringes with both Teflon-coated and uncoated rubber stoppers.

However, shortly after this seemingly minor change, there was an increase in the incidence of antibody-mediated pure red cell aplasia (PRCA) among patients taking EPREX. Pure red cell aplasia is a serious condition in which the bone marrow ceases to produce red blood cells. It took 4 years of extensive investigations involving more than 100 experts from clinical, pre-clinical, manufacturing, process sciences, logistics, quality, analytical, and regulatory fields and in excess of \$100 million to identify the cause. The conclusion was something no one had expected: Uncoated rubber stoppers, when exposed to the new stabilizer, released substances called leachates into the EPREX formulation and that these substances were most likely responsible for the increase in the product's immunogenicity and the resulting increase in patients developing pure red cell aplasia.

It's important to note that the several examples I have given are just some of the many cases in which immunogenicity concerns have arisen. Most biologics have some degree of immunogenicity; their immunogenicity levels can change with even slight changes in their manufacturing process, the consequences of which can be clinically important. And as stated above, immunogenicity can be detected only through clinical testing.

*Clinical Studies May Be Needed for New Uses Despite Same Mechanism of Action*

One significant concern about S. 623 is that it contains a provision stating, "If the applicant has demonstrated comparability for a single condition of use . . . the Secretary shall issue a comparable biological product license for all conditions of use of the reference product sharing the same mechanism or mechanisms of action." This provision presumes that if the drug has the same mechanism in two conditions, evidence of safety in one condition can be used to establish comparable safety in the other. It is important to understand that this presumption is not scientifically correct and could lead to approvals of use in indications in which the follow-on biologic is not safe. While the mechanism of action may be the same for two indications, the patients, their co-morbidities and concomitant therapies may differ.

Once again, the EPREX example is instructive: EPREX is used to correct anemia in patients with cancer and in patients with renal failure. In both patient populations, EPREX and other erythropoietins work to correct anemia through the same mechanism of action: by stimulating more blood cell production in the blood marrow. But PRCA is seen only in patients with renal failure and not in patients with cancer. So if a follow-on version of EPREX were studied only in patients with cancer and found to be "comparable" with an approved erythropoietin, this proposed legislation would allow its use in patients with kidney failure, notwithstanding the possibility that it might have unacceptable immunogenicity in those patients. A similar situation is observed with granulocyte-monocyte colony stimulating factor or GM-CSF, a biologic that stimulates some bone marrow and blood cells. Like EPREX, GM-CSF is immunogenic when used in some diseases and not in others.

These two examples call into serious question the wisdom of approval for all indications with the same mechanism of action after demonstration of comparability in just one indication. Simply stated, if a follow-on biologic is to be used in patients capable of having an adverse immune response to it, it should not be sufficient to study the follow-on biologic only in an indication in which the patients are less capable or incapable of having an adverse immune response to it.

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



2. ANY PATHWAY FOR FOLLOW-ON BIOLOGICS MUST NOT ALLOW FOR DETERMINATIONS OF "COMPARABILITY" FOR PRODUCTS SO DIFFERENT IN STRUCTURE THAT MAJOR SAFETY AND EFFICACY CONCERNS NECESSARILY ARISE

Since it is not possible to make two biologic products identical, follow-on biologics policy will, by definition, allow abbreviated applications for molecules that are highly similar to a reference, despite known or potential differences. However, one must draw a line as to how much of a difference should be allowed as there is no scientific basis for allowing abbreviated testing of a new biologic on the basis of it being only distantly related to an existing one. Some differences are so substantial that the biologics should be considered different products entirely. Some types of known differences are so substantial and so likely to result in clinically meaningful differences, there is no reason not to treat such different drugs as if they are different drugs.

*Differences in Amino Acid Sequence*

One such difference is "minor differences in amino acid sequence," a difference that, according to S.623, would still allow a molecule to be considered "to contain highly similar principal structural features." The amino acid sequence defines a protein. Even a minor difference creates a different (mutant) protein, and a product containing such a mutant protein is a different product from the non-mutant form. Given the enormous potential for such a product to have different effects, any such product should be subject to all the standard safety and efficacy testing to which you would subject any innovator drug.

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

The AspB10 insulin analogue is a prime example. This was a biological product that had only one amino acid difference from the insulin amino acid sequence. At the time it was being studied, it seemed reasonable to think that this insulin analogue would be safe. However, to the great surprise and concern of all involved, when AspB10 was given to laboratory rats, it triggered the development of breast cancers.

In marketed protein products, FDA has never, to my knowledge, allowed a change in even a single amino acid. When a change in an amino acid has occurred during pre-market development, FDA has required extensive testing of the new molecule rather than assuming the properties of the former molecule were retained. To allow marketing of new mutant protein therapeutics with anything short of the testing required of any new protein therapeutic potentially exposes patients to very real risks.

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

*Differences in Post-Translational Events*

As a scientist, I also find it troubling that S.623 would allow products with differences "due solely to post-translational events" to be considered "highly similar" and eligible for demonstration of comparability within the broad statutory definition set forward for abbreviated applications.

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

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

*Complex Biological Products Including Live Viral Products*

Particularly concerning is the provision in S. 623 that “closely related, complex, partly definable biological products with similar therapeutic intent” (for example, two live viral products for the same indication) also be considered “highly similar.” This provision allows abbreviated applications for living cells and organisms and other biologic products far more complex and difficult to define than proteins.

The legislation acknowledges that these biologic products are only partly definable and complex. Therefore, by definition, one cannot know just how different they are. If one cannot know how different the products are, and the possibility exists that they are vastly different, then there can be no scientifically valid basis for determination that they are comparable. The inability to define these highly complex products ought to exclude the possibility that an abbreviated application lacking full clinical testing would provide sufficient protection of safety or efficacy—yet this proposed legislation would allow for that possibility.

Of note in this regard, the legislation cites as an example of closely related products “two live viral products for the same indication.” However, anyone familiar with recent concerns about potential differences in different preparations of smallpox vaccines, of influenza vaccines, and of live polio vaccines will surely appreciate that comparability determinations should not replace full clinical testing for such complex, partly definable products.

*No Limitations Placed*

Finally, I would draw your attention to the fact that after drawing extremely broad boundaries around what types of differences (and what types of products) would fall within the scope of comparability determinations and abbreviated applications, S. 623 undermines even those boundaries. It gives the Secretary leeway to determine *any* two biological products “to contain highly similar principal molecular structure” regardless of known or indeterminate differences. So in essence, S. 623 places no limit on the types of physical and chemical differences that might be considered minor enough to permit a demonstration of comparability and an abbreviated application.

*Language From Orphan Biologics Regulations*

The language in S. 623 describing what differences still leave products “highly similar”—and therefore eligible for demonstrations of comparability (or interchangeability) and for submission of an abbreviated application—appear identical to the language in the orphan drug regulations for biologics, regulations I helped write and implement. While, on the surface, that might appear to make the language a reasonable standard for follow-on biologics, in fact the objectives of the determinations of similarity in the Orphan Drug Act are very different from those for follow-on biologics. Whereas different but related products (for example, those with “minor amino acid differences”) might have similar effects, in orphan regulations, we established a broad regulatory definition ensuring that orphan drug exclusivity would block the marketing of similar molecules even if there were full clinical studies supporting the safety and effectiveness of those molecules. But the fact that two related products with such differences may treat the same condition does not make them the same drug; nor does it provide any significant assurance of a similar safety and efficacy profile. So there is no basis for taking the definitions that FDA developed to preclude approval of products supported by complete data and using them to identify products that can be approved through an abbreviated application with partial data.

3. NO FOLLOW-ON BIOLOGIC PRODUCT SHOULD BE CONSIDERED INTERCHANGEABLE WITH ITS REFERENCE PRODUCT

Given the complexity of biologics, the high potential for process differences to result in product differences, the limited ability to detect differences between a follow-on and reference biologic, and the very real potential for these differences to be clinically meaningful, a determination even of comparability for a follow-on product is particularly challenging. The provisions in S. 623 calling for a determination of “interchangeability”—specifically, that the product “can be expected to produce the same clinical result as the reference product in any given patient”—are very concerning from a scientific perspective.

Ensuring comparability of a follow-on biologic to a reference biologic with an acceptable degree of assurance will be quite challenging, made much more so by the follow-on manufacturer’s limited access to information about, and lack of experience with, the innovator’s process as well as their lack of access to intermediate, in-process materials. Ensuring interchangeability is essentially impossible.

No amount of non-clinical testing of a biologic product can ensure or predict it will have identical effects to another product. Although clinical testing can place limita-

tions on the possible extent of differences, for most products, only extremely extensive comparison studies could rule out clinically significant differences. For example, if a reference biologic caused a serious or fatal effect in 1 patient in 1,000, and a new drug had twice the risk, it would take a study of about 50,000 patients to have a good chance of detecting this important difference. Thus, there is no realistic potential for a scientifically valid determination of interchangeability.

With the risk of clinically important differences always at play, with the possibility that substituting products would increase the risk of clinically important antigenicity, and in the absence of scientific data to establish a follow-on and an innovator biologic product as identical, it would be dangerous to allow the follow-on biologic to be considered “interchangeable” with its reference product.

The European Union rightly acknowledged in its own process of developing a pathway for follow-on biologics that follow-ons can be similar, but never identical to an innovator biologic. After very careful review of the data, the EU recognized the danger of applying “interchangeability” status to follow-ons, a misnomer that could lead physicians and patients to inappropriately assume sameness and substitute one for the other, with potentially serious adverse health consequences. Just 2 weeks ago (Feb. 18), the French parliament, for example, adopted legislation to prevent follow-on biologics from being treated in the same way as traditional generics and banned the automatic substitution of one biologic medicine for another.

A determination of interchangeability likely would encourage substitution of one product for another. The FDA itself expressed concerns about substitution of one biologic medicine for another in a statement last September: “Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response” (<http://www.fda.gov/cder/news/biosimilars.htm>, September 2006). Even if products have a determination of comparability but not interchangeability, substitution could occur, potentially unbeknownst to the prescribing physician or patient and potentially with adverse health outcomes. Policy should attempt to limit that possibility as it addresses issues such as labeling and naming.

Furthermore, if aspects of a follow-on biologics approach such as the designation of interchangeability led to substantial numbers of patients switching between therapies, it could severely impair the ability of pharmacovigilance systems to deal with emerging safety problems. When a new adverse event emerges or a known one increases in frequency, it may be impossible to attribute the adverse event to a specific product if patients experiencing the event have received multiple products. This is especially the case for some types of adverse events, such as those due to immunogenicity, that tend to arise in patients well after receiving the causative product. Should a particular follow-on biologic be associated with such a safety problem, the impact of being unable to determine which “interchangeable” biologic was responsible could be devastating. The ability to detect that a new follow-on biologic has a significantly higher risk would be highly impaired and the difference in risk could go unnoticed. When new risks are noticed, it could well be impossible to determine to which “interchangeable” biologic it was attributable, and appropriate use of the entire group of therapies might be severely impaired because of a safety problem with one.

From the standpoints of science, clear communication, and public safety, interchangeability is not an appropriate designation for follow-on biologics.

Unfortunately, not only is interchangeability for follow-on biologics included in S. 623, the statutory test for interchangeability is completely open-ended. As written, this statutory test could be used to determine that two drugs are interchangeable even if they do not contain the same active ingredient. This is entirely at odds with the concept of “therapeutic equivalence” that has been applied to small molecule drugs and which requires a finding of the same active ingredient, same dosage form and dose, and bioequivalence. If used as the basis for switching patients back and forth between biologics for chronic therapy, then this statutory test poses especially grave clinical implications as patients unwittingly switch between biologics whose safety and efficacy have not been shown to be the same.

#### 4. POST-MARKETING SAFETY SURVEILLANCE WILL ALWAYS BE REQUIRED, AND POST-MARKETING CLINICAL STUDIES MAY ALSO BE WARRANTED

All approved follow-on biologics will inevitably be associated with some risk that new safety problems will become apparent only in the post-marketing period because (1) not all differences between a follow-on and reference product will be detectable in pre-market testing, (2) one cannot predict with certainty which differences may have adverse impacts on safety and efficacy, and (3) some risks of any

pharmaceutical become apparent only after extensive use. To optimize patient safety and to control such risks, it is critically important that FDA not be limited in its ability to request post-marketing clinical studies when appropriate. Follow-on manufacturers should also be required to monitor a product for safety problems through a robust post-marketing safety surveillance program.

Post-marketing clinical studies, post-marketing safety surveillance programs, and drug safety in general have been topics of major discussion on this committee and in these halls. Just last month, Chairman Kennedy and Ranking Member Enzi re-introduced legislation that has as core principles post-approval clinical trials “to assess signals of serious adverse events,” post-approval epidemiological studies to help “screen for serious adverse events in expanded populations,” and post-marketing safety surveillance programs “to assess known serious risks and to identify unexpected serious risks.” Many of you have endorsed this safety bill and applauded these tenets of it.

After all of the support and attention this committee has given to the issue of drug safety, it would be a major setback if this committee were to pass any legislation which does not put forth specific provisions enabling regulatory requirements for post-marketing safety surveillance programs and clinical studies of follow-on biologics, or if it limits the ability of expert reviewers to negotiate for post-marketing clinical studies that could protect public safety.

For instance, S. 623 is silent on the matter of post-marketing safety surveillance, a tool essential to ensuring the safety of all biologics, including follow-on biologics or any pharmaceutical. This should concern all of us. Also disturbing are the specific limits the bill would place on the FDA’s ability to require post-market clinical studies from a follow-on manufacturer. Follow-on biologics will raise safety concerns—such as differences in immunogenicity profile or emergence of unexpected toxicities—that will require studies beyond the scope that pre-marketing studies can reasonably address. We should not prevent the FDA from requiring whatever studies are deemed necessary based on science.

Restricting the FDA in its efforts to carry out its explicit mission of protecting the public health in the post-marketing period would be particularly difficult to explain to the American public given that such protections are already received by the European public. The EU recognized the importance of requiring appropriate safety measures as it developed guidelines for approval of follow-on biologic products. The EU further acknowledged in its guidelines the importance of post-marketing testing for the specific danger of immunogenicity.

Any legislation that fails to articulate the need for post-marketing studies, and instead places limits on the FDA’s ability to seek post-marketing commitments, could lead conscientious regulators concerned about patient safety to require far more extensive pre-marketing testing, thereby significantly undermining the ability of a follow-on approval pathway to address access. Safety would nonetheless suffer anyway. Some safety concerns can be identified only after broad, large-scale or prolonged exposure such as can best be studied in the post-marketing period.

##### 5. THE FDA SHOULD NOT BE SUBJECT TO UNDUE CONSTRAINTS IN ITS ABILITY TO ENSURE SAFETY AND EFFICACY OF FOLLOW-ON BIOLOGICS

Finally, legislation should not limit the FDA’s flexibility and discretion in making sound scientific judgments to ensure the safety and efficacy of follow-on biologics. I have several concerns about S. 623 in this regard.

For instance, S. 623 provides that, when asked, the FDA should meet with follow-on sponsors to “reach agreement regarding the parameters of design and size of the studies” necessary for approval of the application. I applaud this provision but have pressing reservations regarding the binding nature of those agreements in the follow-on context. It is important that agreements not constrain FDA from requiring additional data beyond those pre-specified in advance of the application process. It is to be expected that it will be quite common for the FDA to identify needs for additional testing after initial advice is given for two reasons. First, there are many tests within the general categories of physical, chemical, biological, and clinical testing. To some extent, these tests need to be performed sequentially as the results of earlier tests often identify needs for further testing. The FDA cannot and should not be expected to identify all testing needs up front before early test results are available.

Second, given the lack of FDA experience in reviewing follow-on biologics, reviewers would have no basis for anticipating new data needs that may arise. For these two reasons, it likely will be common that additional testing requirements, important to ensure comparability and thus safety and efficacy, will be identified after initial guidance. While the legislation provides a process whereby the FDA can re-

quest additional testing where a substantial scientific issue essential to approval has been identified and agreed to by the head of the reviewing division, the need to use such a process runs the significant risk of suppressing appropriate testing requests, thus diminishing assurance that the follow-on biologic is comparable.

The provisions under discussion are similar to current provisions regarding binding agreements on clinical trials and on bioavailability and bioequivalence testing (also types of clinical testing) of drugs but differ in a very important respect given the context. Currently existing provisions apply only to clinical testing, and, when the FDA gives guidance on this testing, it already has before it both the results of chemical, physical, and biological testing and it has vast experience in determining appropriate clinical studies. In contrast, the proposed legislation here allows companies to seek binding guidance on all types of testing (e.g., all “studies of a biological product” under these provisions) before any testing results are available, and in an area in which there is no prior regulatory experience.

The FDA should indeed provide industry with extensive guidance as to what testing will be expected in an application and consideration should be given to establishing a transparent process for this to occur. But as we enter this new field with new safety risks, the FDA should be unhampered in its ability to request and receive additional data from a manufacturer as the need becomes apparent. To do otherwise could jeopardize safety.

Another worrisome constraint on the FDA comes in the mandate in S. 623 to the FDA to complete its final review and take final action on a follow-on biologic product application within just 8 months of the manufacturer’s submission of the application. This would be an unprecedented move that places inappropriately high priority on the review of follow-on biologics. Most new drugs and biologics are reviewed with a 10-month deadline to complete review, potentially much longer to reach final action. Even priority drugs and biologics have a 6-month review, and potentially take much longer to final action. The timeline of 8 months from submission to final action is a more accelerated timeline than that for most new drugs and biologics and, in some senses, more than for those given priority drugs. In other words, this legislation gives review of a follow-on biologic priority higher than that for most new drugs and comparable to that for a new and promising AIDS or cancer therapy. This kind of provision inappropriately limits FDA’s ability to allocate its severely limited resources to address the greatest public health priorities. It also runs the risk of giving FDA inadequate time to do its job.

There are other aspects of this legislation with the potential to inhibit appropriate regulatory activity. For example, the proposed legislation specifies that studies to establish comparability should be designed “to avoid duplicative and unethical clinical testing.” The meaning of “duplicative” is unclear; but whereas replication of results is a basic scientific approach to ensure validity, admonition to avoid duplicative testing, depending on how the term is interpreted, could lead to inadequate testing. Regarding unethical testing, the language is unnecessary and could, depending on how it is interpreted, discourage appropriate testing requirements.

#### THE EU APPROACH TO BIOSIMILARS

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

The key features of the EU process stem from the recognition of the unique characteristics of biotechnology derived proteins. Several years ago, EU legislation clearly distinguished a “biosimilar” (the term they use for follow-on biologics) from a “generic” because of the manufacturing principles for biologics that are discussed above. The EU legislation did not attempt to define the scientific standards for approval of biosimilars. The EMEA, the science-based body responsible for approving the marketing of drugs in the EU, was trusted with that task. Furthermore, the EU legislation did not seek to constrain the ability of the EMEA to require data to ensure the safety and efficacy of biologics. The EU legislation clearly distinguished a “biosimilar” from a “generic” due to the many scientific concerns discussed above; the EU also recognized the dangers of interchangeability.

The EMEA provided a broad regulatory framework with guidances for approval of these products. They pursued a science-based, transparent and open process to establish concept papers and draft guidances, starting first with basic principles for all biosimilars. This was followed by more specific guidances with testing requirements for product classes. This transparent process included public scientific work-

shops in which all parties were invited to offer input. The EU testing requirements do allow for abbreviations in testing where science and safety permit. But clinical testing, immunogenicity testing, and post-marketing safety surveillance are critical parts of those requirements. In fact, those requirements were deemed essential to minimize the risk to patients. The EU pathway strives to achieve follow-on biologics that are truly highly similar to a reference product while acknowledging that important clinical differences may still exist upon market approval, making post-marketing clinical studies and safety surveillance important.

#### CONCLUSION

In conclusion, I sincerely hope that the experiences and principles I have discussed have informed this debate. It is my hope that as you examine S. 623 and any other proposed legislative pathways for follow-on biologics, you will seek out and pursue scientifically driven public debate to ensure that public policy is well-founded in science and supports the development of follow-on biologics that are safe and effective. We must ensure that we pay the appropriate attention to the principles of patient safety that are being discussed in this country and in these halls right now.

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

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

The CHAIRMAN. Thank you very much. We might call on Dr. Rossignol, if you'd be good enough. We appreciate very much your taking the time and working with us and this presentation. We look forward to hearing from you.

#### **STATEMENT OF NICOLAS ROSSIGNOL, ADMINISTRATOR, EUROPEAN COMMISSION PHARMACEUTICALS UNIT, BRUSSELS, BELGIUM**

Mr. ROSSIGNOL. Senator Kennedy, can you hear me now?

The CHAIRMAN. Yes, I can. Yes. You're on.

Mr. ROSSIGNOL. Okay. Chairman Kennedy, Ranking Member Enzi and all of the members of the committee, thank you for giving me the opportunity to testify today.

My name is Nicolas Rossignol and I am in charge within the European Commission of the implementation of the framework in Europe on follow-on biologics, which we call in Europe, biosimilars.

If you allow me, Mr. Chairman and without playing with words, I will use the terms follow-on biologic and biosimilars as if they are interchangeable.

It is indeed an honor to appear before you today to share the EU experience in an area which holds great hopes for patients but at the same time, raises new challenges. I will focus today on the key controversial questions around follow-on biologics, which the EU has faced already, which the United States is facing now, hence we are sharing knowledge we've gained that is most useful.

I will not repeat my written testimony but solely focus on three key issues. First is patient safety or to put it bluntly, is it true that follow-on biologics are less safe?

The second question is the question of sameness. Is it true that biologics are so complex that you in any way cannot make copies? And thirdly, interchangeability. Are biosimilars interchangeable?

So let's address first safety. The essential goal of our legislation is to safeguard public health, to ensure that all medicines, what-

ever their legal status, meet the same EU high standards of quality, safety and efficacy. Our framework on biosimilars is no exception. Its primary objective is not to facilitate introduction of new products on the market. It is not to lower standards. The primary objective is to apply equal standards to ensure that biosimilars are equally safe and efficacious, as any other biologics.

Indeed, it is the European Commission which approves all new biotech medicines and we do not approve biosimilars if they do not comply with our standards. Actually, one biosimilar application was already rejected because of non-compliance.

But conversely, those follow-on biologics which do get an authorization, how by definition products for which European regulators are confident to say that they are as safe, as efficacious, as their counterparts.

The second point is the sameness, i.e., can you make copies of biologics? If it's clear that these biologics were no different from chemical drugs, then we would not be using a specific framework on biosimilars in the EU. The current scientific consensus in Europe is that biosimilars are not generics and not biogenetics and cannot be approved as generics. Because these products are complex, we need an abbreviated yet robust set of pre-clinical and clinical data to demonstrate that the biosimilar product is comparable to its reference.

However, it is important, in my opinion, not to over-emphasize the molecular complexity of biosimilars. Yes, these are complex products. Yes, they are usually difficult to characterize but there is a range of complexity. We cannot treat them the same way we treat simple molecules like insulin, for example and far more complex biologics like vaccines. There is no one size fits all approach in this field.

And also and this is the report of my team—molecular complexity is a scientific notion. It does not depend on the leader status of the product. In other words and that may be a myth—we have faith in the past in Europe, biosimilar products, the follow-on biologics are not new products in scientific terms. Biosimilar is just a new legal pathway to authorize their use.

So in other words, biosimilars are just as complex in molecular terms, as their counterparts. They are just as difficult to fully characterize—not more, not less.

The third and last point is interchangeability. Because biosimilars are not generics, medical practices which are standard for generics are not necessarily repeatable here. Like any other biology, biosimilars can carry safety risks which might not be fully detected at the approval stage. I have to say that the framework on biosimilars in Europe does not lead to a scientific conclusion on interchangeability. It doesn't say if a biosimilar product is interchangeable or if it is not interchangeable. Simply because of the construction of the European Union, interchangeability is not a point that our unitization currently addresses. It is addressed to member state schools, not European communities.

However, I want to stress that interchangeability may already occur today in Europe between a number of these products, one innovative product and another one, for example, pharmaceuticals that care professionals may, in some countries in Europe, sub-

stitute one for another one, for example, because they have the same international long comparable name, like insulin again.

Interchangeability is therefore a different notion from comparability that needs to be handled with great caution for all biologics.

Mr. Chairman, I would like to conclude by summarizing what the EU experience tells us in this field. Our experience tells us that a framework on follow-on biologics is not only feasible but is also desirable, to make sure that products on the market are equally safe and efficacious. It also tells us that this framework should allow applications based on a reduced, abbreviated data package to be submitted. That for the very benefit of biosimilar manufacturers, the framework should also be sufficiently robust, science-based and stringent to avoid lowering standards of quality, safety and efficacy.

Our experience tells us that what is at stake here, really, is in fact, the long-time trust and confidence of patients of care professionals in the regulatory system, in follow-on biologics in particular but more worldly by your technology. And we are, of course, prepared to collaborate further with the United States in this emerging, challenging but promising area. Thank you again for this opportunity to testify and I look forward to the questions.

[The prepared statement of Mr. Rossignol follows:]

#### PREPARED STATEMENT OF NICOLAS ROSSIGNOL

Mr. Chairman, honorable members of the HELP committee, thank you for giving me the opportunity to testify today. My name is Nicolas Rossignol. Since 2003 I have been working as an Administrator within the European Commission, in the division in charge of the European Community pharmaceutical legislation. The European Commission has three main roles in the area of pharmaceuticals: it proposes new legislation; it implements existing legislation; and it authorises and monitors the placing on the EU market of certain types of medicines, including all biotech products produced by recombinant DNA technology (*e.g.*, insulin, growth hormones, etc.). The granting of this “marketing authorisation” is done on the basis of a scientific evaluation of the product, which is carried out by the European Medicines Agency (EMA).

Since 2003 I have been responsible within the European Commission for the implementation of the EU Pharmaceutical legislation in the specific field of “follow-on biologics,” which we call in Europe “similar biological medicinal products,” or “biosimilars.” I have been involved in the legal, regulatory and scientific aspects of this topic. It is arguably one of the most complex issues that the European Community has faced in the area of pharmaceuticals in the last 5 years.

My testimony today will focus on how the European Union reviews and approves “follow-on biologics” or biosimilar products. I will address the following issues:

- How and on which principles is the EU legal framework for biosimilars established?
- What regulatory and scientific work has been achieved in the EU since the establishment of this framework?
- What has been the EU practical experience so far with the regulatory environment on biosimilars, and what are the challenges?

#### HOW AND ON WHICH PRINCIPLES IS THE EU LEGAL FRAMEWORK FOR BIOSIMILARS ESTABLISHED?

The notion of “biosimilar product” or “biosimilarity” has been introduced in EU legislation in June 2003,<sup>1</sup> and further elaborated with the adoption of the EU “Phar-

<sup>1</sup>Section 4, Part II, Annex I to Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, as amended by Commission Directive 2003/63/EC of 25 June 2003, Official Journal of the European Union L 159, 27/6/2003. P. 0046-0094.



maceutical Review” in April 2004.<sup>2</sup> This notion allows a manufacturer to submit an application and get an authorisation for a product claimed to be similar to another biological medicine—the “reference product.” The rationale for creating this new licensing route is that biologics similar to a reference product “do not usually meet all the conditions to be considered as a generic.”<sup>3</sup> Although the EU “generic” route remains legally open to biologics (the word “usually” implies that in some cases, generic provisions *might be* sufficient), this is more a theoretical possibility than a practical way forward given the current state of science. It is clear for EU regulators today that the complexity of biological molecules, the fact that they are produced in living organisms and their sensitivity to changes in the manufacturing process make it virtually impossible for applicants to produce an identical copy of a reference biological product. In other words, the licensing route for biosimilars is based on the principles that:

- biologics are not chemical drugs; and
- the generic approach is, in the quasi-totality of cases today, very unlikely to be applicable to biologics: biosimilars are not “biogenerics.”

The regulatory framework for biosimilars is therefore the only one licensing route to be applied to biologics claimed to be similar to a reference product. Three main eligibility criteria can be spelled out:

- First, the product must, obviously, be a biological medicine. In legal terms, this means that any type of biologic could be licensed as a biosimilar, including complex biologics such as blood-derived products, vaccines, gene/cell therapy products, etc. However, the approach is for scientific reasons more likely to be successful today for products which can be thoroughly characterised, such as proteins produced by recombinant DNA technology (*e.g.*, insulin, growth hormones). Conversely, it is more difficult to apply to other types of biologics which by their nature are more complex (*e.g.*, vaccines), or to those for which little regulatory experience has been gained so far (*e.g.*, gene therapy).

- Second, the reference product must have been authorised within the European Community. Importantly, it is not legally required that the reference product is *still authorised at the time* the biosimilar application is filed.

- Third, the application has to be submitted after the expiry of data exclusivity. In the EU, innovative products benefit from a data exclusivity period, which currently varies from 6 to 10 years for old products, and which has been recently harmonised to the so-called “8+2+1” period. This means that an authorised product will get a data exclusivity period of 8 years, after, and only after which a company will be allowed to submit a biosimilar application. However, the actual placing on the market of the biosimilar will not be permitted until 10 years (*i.e.*, 8+2) have elapsed from the initial authorisation of the reference product. In addition, the period will be extended to a maximum of 11 years (*i.e.*, 8+2+1) if, during the first 8 years of data exclusivity, the holder of the reference product obtains an authorisation for new therapeutic indication(s) which bring(s) significant clinical benefit in comparison with existing therapies. This balanced approach has been favoured in order to reward companies who develop innovative products, without impairing the development of the generics and biosimilar industry.

As regards the kind of data required to file a biosimilar application, the EU legislation is based on the principle that a “one-size-fits-all” approach is unworkable in this area. The type and amount of pre-clinical and clinical data are not predefined in legislation but are determined on a case-by-case basis, on the basis of the relevant scientific guidelines. This approach reflects the wide spectrum of molecular complexity among the various products concerned, ranging from relatively simple molecules such as insulin to far more complex ones. Thus, the requirements to demonstrate safety and efficacy of a biosimilar are essentially product class-specific. In theory, a biosimilar application could therefore range from being almost “as abridged” as a generic application (with very limited non-clinical/clinical studies), to being nearly as complete as a full, stand-alone application. The task to determine this range as precisely as possible, concretely and on a scientific basis, *i.e.*, by taking in consideration the characteristics of the concerned products, has been put in the hands of the European Medicines Agency (EMA), to which the EU legislators have given a mandate to issue scientific guidance.

<sup>2</sup>Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, Official Journal of the European Union L 136, 30/4/2004. P. 0034–0057.

<sup>3</sup>Recital (15) of Directive 2004/27/EC, see above.

WHAT REGULATORY AND SCIENTIFIC WORK HAS BEEN ACHIEVED IN THE EU SINCE THE ESTABLISHMENT OF THIS FRAMEWORK?

The first EMEA guideline on biosimilars was released for consultation in November 2004. This was a general, “overarching” guideline designed to introduce the concept of biosimilarity in scientific terms. Since then, a number of guidelines have been issued,<sup>4</sup> most notably on:

- general quality aspects;
- general pre-clinical and clinical aspects;
- product-class-specific pre-clinical and clinical aspects on insulins, growth hormones, erythropoietins and granulocyte-colony stimulating factors;
- immunogenicity of biotechnology-derived therapeutic proteins.

All these guidelines relate to molecules which can be thoroughly characterised with state-of-the-art analytical methods and for which extensive regulatory experience is available.

From a legal perspective, it is not necessary that EMEA issues guidance in one area to enable manufacturers to submit applications. Besides, EMEA guidelines are usually not legally binding—alternative approaches which depart from available guidelines, if properly justified by the manufacturer, may also be accepted. In the case of biosimilars, however, the legislation makes explicit reference to compliance with the detailed guidelines to be issued by the EMEA.

Without going into the scientific details of these guidelines, one important underlying principle is worth being mentioned: to substantiate its claim of biosimilarity, a manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy. Only one reference product is allowed throughout this exercise. Approaches using indirect comparisons (*i.e.*, through other products) are unlikely to be successful from a scientific viewpoint.

The EMEA guidelines make it clear that it is not expected that the quality attributes (*e.g.*, the molecular structure) in the biosimilar and the reference product should be identical. Actually, minor structural differences are reasonably expected given the very nature of biologics and the inherent variability in the way they are produced. However, those differences should in any event be justified on scientific grounds and would be considered on a case-by-case basis, in relation to their potential impact on safety and efficacy. The underlying scientific assumption is that differences between the biosimilar and the reference product are, *a priori*, regarded as having a potential impact on the safety/efficacy profile of the product. They will therefore influence the type and amount of data required by the regulators in order to make a satisfactory judgment of compliance with EU standards. For example, changes in glycosylation patterns are well known for having potential effects on the safety/efficacy profile of glycosylated proteins.

In case the reference product has more than one therapeutic indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product, but this is not automatic (it may also be that the biosimilar applicant does *not* claim all the therapeutic indications of the reference product). Justification will depend on a number of factors, such as clinical experience, available literature data, etc. In essence, regulators’ judgment to approve therapeutic extrapolation is again product-specific.

WHAT HAS BEEN THE EU PRACTICAL EXPERIENCE SO FAR WITH THE REGULATORY ENVIRONMENT ON BIOSIMILARS, AND WHAT ARE THE CHALLENGES?

The EU framework on biosimilars is relatively new. Two products have been authorised so far under this framework<sup>5</sup>: the first is the growth hormone Omnitrope, which was authorised by the European Commission in April 2006. A second growth hormone, Valtropin, was also authorised in April 2006. One product (Alpheon, an interferon) was given a negative scientific opinion by the EMEA in June 2006.<sup>6</sup> One of the main reasons for this is that the EMEA had major concerns regarding the comparability of Alpheon and its reference product (Roferon-A), be-

<sup>4</sup><http://www.emea.europa.eu>; in addition, a guideline on pre-clinical and clinical issues related to a biological substance of extractive origin (Low Molecular Weight Heparins) is also in preparation.

<sup>5</sup>The register of medicinal products for human use authorised by the Commission is available at <http://ec.europa.eu/enterprise/pharmaceuticals/register/alfregister.htm>.

<sup>6</sup><http://www.emea.europa.eu/pdfs/human/opinion/19089606en.pdf>.

cause of differences identified between the two medicines, such as impurities. The EMEA was hence of the opinion that Alpheon could not be considered as a biosimilar.

A number of additional applications are already in the pipeline at the EMEA. They mainly concern erythropoietins (EPOs), interferons, insulins and granulocyte-colony stimulating factors (G-CSFs). An early dialogue between the manufacturers, the EMEA and the European Commission has proven critical to sort out the various regulatory and scientific issues that applicants may face.

Open debate with all stakeholders has proven extremely useful to gather input, compare experience and build consensus, in particular when drafting guidance documents. As science evolves, our ability to better characterize biologics should increase, as well as our regulatory experience with these products. One can therefore expect, in the long term, that the “range of possibilities” (types of biologics for which the biosimilar approach is scientifically acceptable, amount of clinical data required to demonstrate biosimilarity, etc.) will become more and more precise.

The “legal construction” of the European Community assigns certain competences to the European Commission, while some others are for the Member States. The issue of pricing and reimbursement, in particular, is basically of national competence in Europe. Therefore the EU harmonised regulatory framework on biosimilars does not address this issue. Given the limited number of products authorised so far and the fact that this framework is quite new, it is probably too premature to assess the actual impact of the introduction of biosimilar products on the price of biologics in Europe. However, this is a parameter the European Commission is likely to monitor with particular attention in the coming years.

Some new issues have fueled the EU debate on biosimilars in the recent past. One of them relates to interchangeability between biosimilars and innovative products. It is important to bear in mind that the EU regulatory framework on biosimilars is designed to achieve one objective: to assess the quality, safety and efficacy of biosimilars so that these products comply with the same EU health standards as any other medicine. This framework, however, is not legally designed to evaluate whether a biosimilar is actually interchangeable in medical practice with the reference product, *i.e.*, whether one product can be safely substituted for the other and have the same biologic response without triggering adverse reactions. Interchangeability is also beyond the scope of the existing EMEA guidelines on biosimilars.

Finally, one last point in discussion today relates to the naming of biosimilars. Medicines usually have an International Non-proprietary Name (INN) (*e.g.*, “insulin”) which is defined by the World Health Organisation. Generics usually have the same INN as the reference product, and healthcare professionals often prescribe by INN. The biosimilar industry has been advocating that a biosimilar product, once proved biosimilar, should be entitled to have the same INN as its reference product. On the other hand, the innovative industry has claimed that a distinct INN should be assigned to biosimilars, in particular for the sake of traceability and pharmacovigilance. Our understanding within the European Commission and EMEA is that the rules of the INN naming system should remain international, science-based rules. The same scientific rules should apply to all products, be they innovative products or biosimilars. The INN nomenclature should not be used as a way to distinguish between biosimilars and other types of products.

#### CONCLUSION

Overall, I believe it is fair to say that the flexibility of the EU regulatory framework on biosimilars has been positively welcomed by both sides of the pharmaceutical industry. The fact that the legal basis is relatively concise and focuses on the key legislative elements of this framework, while technical aspects are addressed through guidelines, has enabled us to undertake a cautious and balanced, “not too stringent, not too loose” approach to allow biosimilar manufacturers to get streamlined access to market, without compromising public health. The defining principles which have guided us so far in regulating biosimilars will remain crucial to address the challenges still ahead of us. Our primary objective should remain to protect public health: biosimilars should meet the same standards of quality, safety and efficacy as any other biological product in the EU. Our regulatory framework should remain based on science: it should fully take account of the fact that biologics are, in the vast majority of cases, not simple molecules. And finally, our experience over the past few years demonstrates, I believe, that transparent and open dialogue with all sides of the industry is key to put in place a robust and adapted regulatory framework in this emerging field.

Thank you.

The CHAIRMAN. Good. Thank you very much, Doctor. We appreciate your staying with us here for the question period. Thank you.

Dr. Hussain, we thank you very much for your presence and look forward to hearing from you.

**STATEMENT OF AJAZ S. HUSSAIN, PH.D., VICE PRESIDENT AND GLOBAL HEAD OF BIOPHARMACEUTICAL DEVELOPMENT, NOVARTIS, PRINCETON, NEW JERSEY**

Mr. HUSSAIN. Good morning. I am Dr. Ajaz Hussain, Vice President and Global Head for Biopharmaceutical Development at Sandoz. I want to thank Chairman Kennedy, Senator Enzi and other distinguished members of the Senate HELP Committee for giving me this opportunity to represent Novartis Group of Companies.

As a former research scientist, as a regulator at FDA, which dealt with interchangeability in these issues on a daily basis for about 10 years and as an American, who has at various points in my life also been a patient, I believe in the Gold Standards of the FDA approval process and want to see only safe and effective medicines made available to patients. I believe this is achievable for follow-on biologics as it is for all the drugs and biologics.

Novartis supports—strongly supports a balanced position which advocates that the same standards of high quality and science be applied to all medicines and that there be respectful, legitimate intellectual property. We recognize a role that generic drugs play today and follow-on biologics will play tomorrow in our healthcare system.

We believe the following are critical in any follow-on biologics regime. One, follow-on products can be made or designed to be used interchangeably with the original product. That's what is meant by interchangeability. Science shows that the same product can be made in different ways. That is what we mean when we say a product is not the process and this is what we mean by comparable products.

Three, every clinical step necessary to bring in new biologic market is not needed to show that a follow-on is as safe and as effective.

Four, here is the good news, Senators. You don't need to choose what specific steps are required. FDA already has the expertise to do this as shown by their approval of innovative products. What you need to do is to empower them to act and that was one of the frustrations I had with the policy development team, is to get stuck with not being empowered to do this.

In the debate so far, you have been hearing essentially two opposite ends of the spectrum on the issue of follow-on biologics. Some say follow-on biologics are impossible and inherently dangerous and you can see the shift in bad direction already occurring but that position has moved to yes, it's possible now.

Others have argued that you should simply apply the generic drugs model. Novartis believes that there is a viable and responsible solution compatible with the current state of science, a middle ground. We believe it is time for an explicit regulatory pathway. The science is here and has been for at least a decade. With all due respect to my colleagues who don't share this perspective, the evi-

dence that the science is here is the existence of the reference products themselves. Clearly, these products can and are being made and indeed, we have marketable versions of many biologics already on the market, independently developed, independently approved but also successfully in use for the same indications.

Comparability is not a new concept, especially for the biopharmaceutical industry. Our ability to make and characterize biosimilar products and other complex biologics has progressed rapidly in the last few decades. Comparability itself is not new. It has enabled manufacturing changes without complete clinical trials for over a decade. It is a signs-based regulatory success story. It also proves that product is not the process.

Some suggest that products have to be the same. However, batch to batch variation is inevitable for all biologics and as long as manufacturers ensure that subsequent batches stay within the same goal post of acceptable variation when the product is made available to patients.

Comparability principles can likewise be enforced on follow-on biologics and unintended consequence of protectionism disguised as sameness is that it raises the hurdles for innovators and makes products for unmet medical needs increasingly unavailable to patients.

Interchangeability is an important public health goal and a natural next step. All that is needed is a small step, a natural progression. Using public prior knowledge, a follow-on sponsor submits data comparing their candidate to an approved product. FDA already uses comparability data for manufacturing changes and there, interchangeability is presumed.

The small step is allowing it for follow-on products by a different sponsor. Everything else follows. No access to innovative data is required.

In conclusion, Novartis applauds the leadership of the Senators of this committee on this issue. We support a thoughtful, balanced approach based on established signs of comparability that makes safe and effective follow-on biologics available. Ultimately what matters is a safe and successful outcome for the patient. Thank you.

[The prepared statement of Mr. Hussain follows:]

PREPARED STATEMENT OF AJAZ S. HUSSAIN, PH.D.

Good morning, I am Dr. Ajaz S. Hussain, Vice President & Global Head of Biopharmaceutical Development at Sandoz. I want to thank Chairman Kennedy, Senator Enzi and the other distinguished members of the Senate HELP Committee for giving me the opportunity to represent the Novartis Group of companies (“Novartis”) at this hearing. As a former research scientist, as a regulator with 10 years of experience at the FDA—where I was Deputy Director of the Office of Pharmaceutical Sciences until October 2005—and as an American who has at various points in my life also been a patient, I believe in the “Gold Standard” of the FDA approval process and want to see only safe and effective medicines made available to patients. I believe that this is as achievable for follow-on biologics as it is for all other drugs, generic and innovator, including biologics.

Novartis is a world leader in the research and development of products to protect and improve health and well-being both by developing innovator drugs and biologics, and also by making generics available once patents have expired. Novartis is unique among pharmaceutical companies because it has made large investments in both branded and generic drugs. Given this, our position on follow-on biologics is not based on the commercial interests of one particular product. Instead, Novartis strongly supports a balanced position, which advocates that the same standard of

high quality and science be applied to all medicines, and that there be respect for legitimate intellectual property, while recognizing the role that both generic drugs and follow-on biologics can play in the health care system. Novartis' success as a global leader of the innovator biopharmaceutical industry is demonstrated by the approval and launch of 15 new molecular entities in the United States since 2000—more than any other company. Novartis' global research base, the Novartis Institutes for Biomedical Research, is located in Boston, Massachusetts where 1,300 researchers work towards developing the next generation of therapies. We also are relocating our Novartis Vaccines and Diagnostics Division Global Leadership to Commonwealth of Massachusetts in the third quarter of this year, and will be bringing together hundreds of additional researchers to develop the next generation of vaccines.<sup>1</sup> We are committed to a future of innovation and new medicines, but we also believe in free markets and competition, and we are not afraid of them.

In the debate so far, you have been hearing essentially two opposite ends of the spectrum on the issue of follow-on biologics. At one end of the spectrum, some have argued that follow-on biologics are impossible and inherently dangerous, while others suggest that this is just a re-run of the 1984 debate when generic drugs were said to be impossible too and that everything we need to develop such products can already be done today. And the former, those adverse to follow-on biologics, do not accept that interchangeable products can ever be produced by other than the original manufacturer. In such a polarized context, Novartis appreciates this opportunity to share an alternative perspective; one that we believe encompasses a viable and responsible solution compatible with the current state of the science.

In considering this public health issue, we start from the premise that follow-on biologics are essential to the future economics of health care both in order to stimulate innovation, and, as important, to ensure that patients have access to the medicines they need at affordable prices. That a fair solution can enable both the innovator industry and the generic industry to prosper such that patients can benefit across the board, is a concept too often lost in this debate as both extremes try to pursue their respective “wish lists.” For its part, Novartis believes that a balanced solution is possible, one that will provide greater access to safe and effective medicines through the availability of competitively-priced biologics when patents expire. Toward this end, Novartis believes it is time for an explicit regulatory pathway that encourages the development and approval of follow-on biologics, including interchangeable products.

We define follow-on biologics broadly to include comparable versions of already-approved biologics and also improved versions of current therapies that depend on the same mechanism of action are used in the same indications as the originator product, and are developed based upon an extensive and sound set of data generated by the subsequent sponsor, which includes stand-alone product and process development and the demonstration of comparability with the reference product on all relevant levels, that is, chemical, pre-clinical, and clinical (including immunological) and appropriately qualifying differences.

#### THE SUCCESS OF THE BIOPHARMACEUTICAL INDUSTRY DESERVES COMPARABLE REGULATORY PROGRESS

The biopharmaceutical industry has made phenomenal progress since the first biotechnology-based medicine was licensed in the United States in 1982. Technologies to make and characterize protein products and other complex biologics have progressed rapidly in the last two decades, and the use of comparability to facilitate manufacturing changes has become established by innovator companies and regulators around the world since FDA led and then first formalized the concept in the United States in 1996 with the Comparability Guidance. Comparability allows for flexibility in the development of products that is essential to their optimal manufacture and iterative improvement. It is a science-based regulatory success story, with very few exceptions.

Significant and continual advancements in scientific disciplines such as analytical characterization, product and process design, process control, and clinical assessment based on underlying mechanisms of action provide a sound scientific basis to utilize the fundamental principles and procedures of comparability evaluation for follow-on biologics. We are confident that this science-based approach will enable the industry to progress to the greater availability of affordable biologics to which we all aspire.

<sup>1</sup>Note that the Novartis Corporate Headquarters are in New York, and Novartis has facilities in Arkansas, California, Colorado, Georgia, Massachusetts, Michigan, Nebraska, New Jersey, New York, North Carolina, and Wisconsin with total U.S. employees numbering 29,000.

In supporting a new regulatory pathway based on comparability such as that described in the "Access to Life-Saving Medicines Act," Novartis is merely recognizing the next logical step in the evolution of the biopharmaceutical industry. The biotech industry is a success story with multiple blockbuster products and well-capitalized companies, as well as those small and emerging companies that hopefully will contribute to its future. Its very success, creativity, and growth, since insulin was approved as the first biotechnology product back in 1982, is what makes this next step possible. With key patents expired and expiring, the time is appropriate to enable greater access to these medicines.

In proposing that the development and approval of follow-on biologics be enabled, Novartis is drawing on its own decades of experience as well as its current capabilities and portfolio across the full breadth of the biotechnology and pharmaceutical industry. While care must be taken and standards maintained, the dramatic progress in biotechnology has already enabled development of the first follow-on biologic products. Indeed, some would say the entire industry is already a follow-on industry because most of the first-generation biotechnology products themselves were follow-ons to their naturally-sourced counterparts. We believe that this great success achieved by the biopharmaceutical industry working with the FDA regulatory experts should be the bridge to an even greater future. We envision the advancement of public health through the increased therapeutic options that become available and are accessible when follow-on biologics are approved through the appropriate application of the new regulatory pathway. Just as we trust the FDA to judge the appropriateness of comparability for innovators, so we can trust them to apply the same principles carefully and responsibly to all other sponsors.

#### INTERCHANGEABILITY IS AN IMPORTANT PUBLIC HEALTH NEED

A regulatory pathway that encourages the integration of appropriate public prior knowledge, as well as one that enables a subsequent sponsor to submit data comparing their candidate to a previously approved product, are natural progressions in enabling the safest and most effective products to be made available to patients. Moreover, just as comparability for innovators' products pre- and post- any manufacturing change has presumed interchangeability to their final product, so the potential for interchangeability of a product from a subsequent sponsor, who has demonstrated comparability to an existing product, must be a legitimate consideration if not a foregone conclusion.

The industry and FDA accept that batch-to-batch variation is inevitable for biologics, and, as long as manufacturers ensure that subsequent batches stay within the same "goal posts" of that accepted variation, then the product is made available to patients. Comparability principles ensure that, for biologics, the same rules apply for after-approval manufacturing changes, and they can likewise be imposed on follow-on biologics. In none of these cases is "sameness" a useful or scientifically-valid concept, any more than it has been at any time for any biologic. To argue otherwise (for example insisting on "sameness" requirements that are not the current regulatory standard) creates hurdles to follow-on biologics that are greater than those required for innovator products and counter-intuitive. Similarly, an unintended consequence of such protectionism disguised as "sameness" raises the hurdles for innovator products, and makes products for unmet medical needs increasingly unavailable to patients. What we need are consistent and appropriate regulatory standards applied to all biologics independent of their sponsor.

In addition, a regulatory pathway that allows any sponsor to further innovate and develop a new second-generation product that is expressly different from but related to the first-generation product, and that represents an improvement in the medical options for patients, can be enabled by a pathway based on principles of comparability. This element encourages second-generation biologics but is precluded in the European approach and yet may represent significant opportunities in the "Access to Life-Saving Medicines Act."

#### BIOTECHNOLOGY MEDICINES HAVE THE CONFIDENCE OF THE PUBLIC

It is essential that the high standards for safety and efficacy that patients expect and that the biopharmaceutical industry has provided in collaboration with FDA are maintained through appropriate and consistent regulatory requirements for *all* biologics. These standards have been achieved through the application of rigorous, science-based regulatory requirements by experts for over a century under the PHS Act. The current statute reinforces the requirements for safety, purity and potency. However, just as we trust the FDA to assess the unknown (new) biologic about which we necessarily have the least experience, (namely the innovator products), using these criteria, so too we can entrust the Agency to evaluate follow-on biologics

which refer to products for which we now have decades of experience. We believe Congress should confer on FDA the flexibility to accommodate progress in science, and help enable the regulatory requirements to evolve appropriately as well. As such, FDA can, through public notice-and-comment rulemaking, and guidance as appropriate, implement a comparability-based pathway for follow-on biologics without requiring arbitrary, unnecessary or unethical duplication of pre-approval studies or clinical trials, and by allowing appropriate extrapolation between indications based on mechanism of action. We can also allow FDA to use their experience with comparability to evaluate a follow-on biologic sponsor's data, and judge the appropriateness of the products being designated as interchangeable—all while recognizing that FDA does not regulate the practice of medicine. The EU may have chosen to defer to member States on interchangeability (the EMEA has not rejected interchangeability for biosimilars as some have misrepresented), but the history of generic drugs in the United States makes it much more fitting that FDA recommend the designation—they have the skill and the public health responsibility that make this appropriate. It should also be noted that, throughout this process, no access to the innovator's data is required—the approval of the follow-on biologic can rest solely and surely on the shoulders of the subsequent sponsor's comparative data which it obtains by running side-by-side studies of the innovator reference product and its own follow-on biologic.

#### PROTECTION OF INTELLECTUAL PROPERTY IS THE LIFEBLOOD OF INNOVATION

Strong intellectual property protection, including patents, trade secrets, and confidential information, is essential to promoting innovation that results in new therapies to meet patient needs. However, Novartis believes that, by having a regulatory pathway that allows more rapid and efficient realization of this innovation through greater use of comparability and prior knowledge for second-generation products as well, these IP rights are enhanced not undermined by a follow-on biologics pathway. Moreover, with each follow-on sponsor developing its own independent data package, and not relying on the innovator's data, we believe these property rights are respected even for those products on which the patents have expired and competition appears imminent. Historically, the biotech industry has established robust patent estates. However, when these patents expire (including patents claiming those PHS Act products for which up to 5 years of patent-term restoration already has been granted under existing Hatch-Waxman), increased competition and access to safe and effective medicines should proceed in the free market. Litigation over patents will still occur, but those litigation proceedings should, and in fact do not need to be coupled to the regulatory approval process. Nonetheless, Novartis is prepared to work with the committee and its staff to develop appropriate legislative provisions that would apply at the conclusion of the FDA approval process. Such a process for follow-on biologics could include a 45-day notification of an issued approval, during which time the innovator would be alerted to an approval referencing its product, and the innovator could institute litigation if it believed that its patent or other intellectual property rights have been violated.

Novartis believes that, if follow-on biologics are to become available to patients in a timely manner, it is essential to “decouple” patent litigation from the approval of new products using a comparability-based regulatory pathway. The complexity of biotechnology product patent estates is such that we do not believe waiting for resolution of biotech patent litigation in the Courts will be other than a barrier to the timely availability of follow-on biologics. Consequently, we believe companies should be able to decide how best to approach the market if they believe there are not outstanding patents, or that any patents still in force are invalid or not infringed just as they can for any PHS Act biologic today.

In legislating this “decoupling,” it may be appropriate for Congress to consider other mechanisms by which to make the exclusive marketing window more predictable for innovators. Novartis supports a non-patent research incentive such as may be achieved through modeling on EU data exclusivity provisions, more appropriately called market-exclusivity provisions, for innovator biologics approved after enactment of any new legislation, as a way to enhance regulatory certainty for all sponsors (which would be independent of the patent estates). Such an approach would prevent diversion of excess resources being used by either innovators or the sponsors of follow-on biologics on slow and expensive patent litigation, and enable those resources to be dedicated to the development and new and more efficient manufacturing of biologics. However, beyond harmonizing this one discrete component of the EU system, in general, the EU approaches on follow-on biologics *per se*, their so-called “biosimilars,” suit an EU environment of 27 distinct countries with different legislative and regulatory histories as well as very different health care and reim-



bursement systems. The United States needs a solution that suits U.S. needs and statutory environment as it has been evolving here for over 200 years following adoption of the U.S. Constitution.

THE DEVELOPMENT OF NEW REGULATORY REQUIREMENTS MUST BE TRANSPARENT  
AND THE RULES FAIR

For any new regulatory pathway, the FDA will need to go through a process of developing regulations. While promulgation of regulations need not be blocking applications in the meantime, their development can be expected to facilitate the choices for those sponsors and patients who can afford to wait a little longer. The FDA has a mission to enhance the public health, and follow-on biologics will be part of that as a result of enhanced patient access and competition. Novartis supports such an open process, while not accepting that it should ever serve to block follow-on biologics while the regulatory implementation process proceeds. Unlike the EU, the United States has a long established and very accessible public participatory process, in which submissions to dockets are available to the public. It will be through this notice-and-comment rulemaking, as well as the development of guidance, to which the experienced innovator industry and others will be able to contribute and ensure that only safe and effective follow-on biologics are approved.

CONCLUSION

Novartis envisions a win:win public health and public policy solution whereby a follow-on biologics industry is enabled, patients get greater access to high-quality and improved biotechnology products at competitive prices, and that provides innovators relief from outdated requirements and a less burdensome pathway to improve existing products. As recognized by the FDA leadership, it is not appropriate to use outdated regulatory requirements just because those parameters were considered historically useful. In this and other important regards, the opportunities to innovators through the creation of a new regulatory pathway based on comparability such as, for example, in the "Access to Life-Saving Medicines Act," should be at least as great as any available to generics, especially with respect to second-generation products. We do not believe that this is a zero-sum game. PHARMA's own numbers say 418 biotechnology medicines are in development, and yet, only 4 recombinant PHS Act applications were approved in 2006. It is time for all of us to work with FDA to improve the review for all biologics such that every patient can get access to safe and effective medicines that will compete in the market place and be more affordable, while also encouraging the development of the new therapies which are so desperately needed.

The CHAIRMAN. Thank you, thank you very much. We try to do 5-minute rounds, if you would, please.

Let me ask the whole panel a question to get your reaction. Recently, I had the good opportunity to meet with a number of the major biotech industries in my own State and I was interested in the coming together after a good deal of debate and discussion, around the idea that there was a pathway to move on this, as long as it was basically driven by the science, protect safety and also promoted the innovation and that it was feasible. Let me ask each of you, what are the specific recommendations that you'd have for us to achieve that pathway? If you'd be good enough.

Mr. BANWART. Chairman Kennedy, from our point of view, we reiterated the five principles in my testimony and we think it is important that the FDA be authorized to use their innovation and their scientific knowledge to pursue the pathway to follow-ons. So we think the most important aspect there is the enabling legislation that would allow the FDA to do this job and in addition, to provide them the resources to do the job. So it's—in our view, it's a matter of the what and the enabling legislation to create the what.

The CHAIRMAN. Dr. Siegel.

Dr. SIEGEL. Well, I'd say that the considerations are—the most important considerations are largely those I mentioned in my ad-

dress. I think we really do need to have good public debate to bring the science out. I think this hearing is a terrific step in that direction. I commend the European model and approach in that regard. I think it is important that we not go beyond the science. You can't just take a molecule that has never been in people and that you can't be sure what it is and all of a sudden, market it to thousands of people. It's too risky. You need to identify what the risks are, you need to do the appropriate clinical trials. You need to ensure that the FDA is fully empowered to ask for the data and the types of studies it needs. You can build a policy based on high degrees of similarity but you should not apply that policy to products that are not highly similar, to products that are so complex that you couldn't determine if they are highly similar and you should not say that similar things tell you that they are the same. It's an important difference and it's an important difference in how we practice medicine. Legislation and policies should take that into account.

The CHAIRMAN. You believe that FDA has the knowledge and the know-how and the ability to do that, at the present time?

Dr. SIEGEL. I think the FDA does. I think it will be a learning process. I think there are certain—in the legislation before this committee at the present time, there are certain constraints on the FDA's ability to ask for studies that it needs, both post-marketing and pre-marketing. There are timelines for the FDA to reach complete decisions whereas typically in legislation, there are timelines for FDA to have complete reviews and if more data is needed, to ask for it. In this legislation, it constrains the ability to ask for data. There are certain types of studies that can't be asked for. So I think the FDA has developed to the type of expertise. I think it will learn as it goes. I think it needs to be given the opportunity to set appropriate standards and to do this the right way.

The CHAIRMAN. Good. Dr. ROSSIGNOL, Senator Schumer indicated earlier in his presentation, there are different marketing techniques obviously in Europe and exclusivity is 11 years. They have effectively about half the profit in terms of innovation that American companies have. Would you comment on whether you think we should look at 5 years, if they have 11 years? Is there a relationship there? If you would make just an additional comment on that. And then I'll ask Dr. HUSSAIN to make a final comment and my time will be up.

Mr. ROSSIGNOL. Thank you, Mr. Chairman. In response to the first question, I would simply name three criteria. First I think, from our experience in the Union, I would have to say is a short experience. I mean, the framework on biosimilars or follow-on biologics was created really in 2003 so its only 4 years but I would say first that we had to be cautious and not to create something that would be too flexible or not stringent enough and that could then spread suspicion on the actual safety and efficacy standards of all biotech products. First start cautious, I think is one key point. The second key point is that the framework should be flexible and adapted to the type of products. When you talk about pilots, this is a big world and you have to separate and distinguish between those biological products that can today characterize relatively well, like small proteins, like insulin, growth hormones and

you have to distinguish these from more complex products. In Europe today, take vaccines for example, we don't believe scientifically that a biosimilar approach would be appropriate for these products, simply because its very difficult to characterize them.

The third point is really more a point of procedure and constant dialogue with all the stakeholders. I think this has been instrumental and key now in our context, in the European context to discuss both sides of industry and to actually gather expertise which primarily lies in the companies today because this is a relatively new field.

Regarding the exclusivity provisions, i.e., your second question, Mr. Chairman, I think I will respond in a general way. We do have specific provisions for data exclusivity in Europe to protect innovation, to reward innovation and I have put some information together in my written testimony and I will be more than happy to provide further information on this. But I have to say that this is one context, which is the European context, which is very specific, especially in terms of pricing and reimbursement. So as a general comment, I would say that this context has to be taken into account when reflecting on applying our framework somewhere else in the world.

I think that you have to distinguish between the science and rewarding innovation, idea rights, et cetera. The science is presenting everywhere and there is no reason why, in principle, scientific requirements should be different on one side of the Atlantic than on the other. And in this respect, on science, we already have ongoing collaboration with the FDA. We believe they have the appropriate expertise to assess these types of products and we are absolutely prepared to continue collaboration and to extend our collaboration in this respect. But this is all science and science should be the same everywhere.

But protection of innovation, rewarding innovation and the balance between innovation and access to affordable medicines is something, in our opinion, that has to be seen in the context, in a specific national context, which is different in Europe than in the United States.

The CHAIRMAN. Thank you. Very helpful response. My time is up but I want to ask Dr. Hussain, if you'd maybe just respond to the first issue.

Mr. HUSSAIN. Mr. Chairman, I'll be brief. I just want to make two points before I sort of give you the answer. One is, I think as a quote/unquote General Company Sandoz is a new era company also at the same time. We want to bring innovative solutions to making interchangeable biosimilar products, follow-on biologics. In that regard, we have invested, as an example, in MIT technology to really seek and discover hybrids—that's just one piece of the puzzle. The reason I say that is, the solution to this challenge is, you have to empower FDA because FDA has to judge the science on which our applications will be based on. This is proprietary science and technology and you can hear my perspective and my colleague's perspective but the solution will be with FDA. So FDA has to judge the science. FDA has to ensure the safety and FDA has to recognize innovation because we bring innovative science and technology to be interchangeable. And I think the only solution

is to empower FDA. So from that perspective, I think, as one of the frustrations I had—I led the policy development for 3 years on follow-ons myself and the frustration was lack of involvement.

The CHAIRMAN. Thank you very much.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman and I've really learned a lot today and I have a lot of questions as a result of probably misunderstandings and I will submit many of those in writing and I hope that you will respond to them as promptly as possible. Is Mr. Rossignol still with us?

The CHAIRMAN. Yes, I hope he is still on. We have to thank our technicians here. This is a wonderful opportunity to hear from—it was a wonderful opportunity.

[Laughter.]

The CHAIRMAN. It is and we thank you.

Dr. ROSSIGNOL. I can still hear you.

Senator ENZI. I thank you for rejoining us. I do like the term, biosimilars and I notice that it is not bio-sames. I understand that vaccines and plasma proteins are excluded from the biosimilar law in Europe. Could you discuss why it was decided that they should be excluded from the European Commission law?

Mr. ROSSIGNOL. Thank you, Senator Enzi. Well, actually they are not excluded. I think that there is a difference in Europe between the actual legal framework and the current scientific consensus and I want to stress three words—current scientific consensus. If you talk only about the legal system, actually our legal system first does not preclude the theoretical legal possibility that the biologic—any biologic—could be authorized as a generic. So that legal possibility is foreseen in EU education. However, when biological product does not meet the conditions of the generic, then you have the biosimilar framework. So that's the legal construction.

If you talk about science now and the current scientific consensus in Europe—the current scientific consensus is that realistically, this framework on biosimilars can only be applied to products which can be thoroughly characterized and I should also add for products for which we have already in-depth regulatory and clinical experience. So to give you some concrete examples, the small proteins I named already—insulin, growth hormones, interferon, to a certain extent, alpha proteins—these types of products which are relatively simple molecules can be already today relatively solely characterized, and are considered in Europe, as being eligible scientifically to the biosimilars. For the others, although legally they are eligible scientifically, the consensus is that they are basically so complex that it's not appropriate today, given the current state of science, to approve them under this legal pathway. Is that clear?

Senator ENZI. Very helpful, thank you. Dr. Siegel, I appreciate your testimony. I did note that you do not support the Clinton-Schumer bill as it would put unsafe products on the market. I think I got that right. Others have indicated that no clinical trials are required when innovative manufacturers initiate a new manufacturing process. And therefore, there should be no clinical trials for follow-on biologics. Can you explain the differences between changes in the manufacturing process for an innovator and the cre-

ation of a manufacturing process required for a generic to create follow-on biologics?

Dr. SIEGEL. Yes. First let me say the premise of that question really—others have said that but it's based on a misunderstanding. When innovators make manufacturing changes that come anywhere close to the types of the changes that would be implicit in having a new manufacturer, they are required to do clinical trials. They often, in fact, avoid making such changes. I can speak now from the innovator side of the equation as well as from the regulator side of the question because they recognize that those major changes in how a product is made do potentially change the product and it means that they will need to do studies and there will be a significant likelihood that those studies will show that the product isn't the same. So that's driven by the science. The types of changes you see, for example, an innovator—you'll see with the follow-on biologic is the use of a different master cell line, a master cell bank and cell line and that is something an innovator would almost never do and regulators would only permit, with substantial testing and often discouraged, changing the manufacturing facility, changing the process. These are major changes.

There are also important differences between how an innovator changes their process because there can be important changes in a final product that can't be detected in the final product. If you have a new contaminant or a new variant of a product, you may see it in large amounts in what is initially made by the cells, even less so once that's been purified and even less so once that's been formulated because formulation can interfere with certain testing. But the purification process can bring contaminants and variance down to levels that are below detectability but are still important. So an innovator will look at every stage of process for what's changed or different, understands the process, knows what's important in the process, knows what needs to be controlled, what variations in a protein are critical and what are not. So there is a tremendous knowledge base. There is access to materials. There is understanding the testing but there is also just an extent of changes that will go on with the follow-on that are large and that, in fact, do require innovators to do clinical testing as well.

Senator ENZI. Thank you. This is extremely complex and my time has expired. I do have several questions for each of you and I will submit those. Thank you, Mr. Chairman.

The CHAIRMAN. Senator Clinton.

Senator CLINTON. Thank you very much and I want to thank all of the witnesses, those who are present here and Dr. Rossignol, thank you for being with us by long distance. This has been very impressive and important testimony.

I think we all agree that safety is paramount. That is the bottom line and what the testimony today highlights is the need for greater FDA post-market authority across the board. The Waxman-Schumer-Clinton legislation was written to reflect the current reality with regard to post-market studies on the brand side. There are no post-market studies because the FDA does not have the authority. So if the reality does not provide great enough safety assurances, then we should raise the standard across the board and provide FDA with an enforceable authority to require post-market

studies on both brands and follow-on biologics. Clearly, when changes are made in the existing manufacturing process or facility, as Dr. Siegel said, that raises questions, which is one of the reasons why the innovators don't do it. Well, that seems to me to be somewhat backwards because if there are needs to make such changes, the FDA should be empowered to act in a more expeditious manner in order to facilitate such changes.

So in effect, we have tied the hands of the FDA, both with what could very well be legitimate changes in the innovators processes and facilities or cell banks or lines or whatever else has to be changed in the opinion of the innovator to bring a safe and efficacious product to market and we don't have the authority for the follow-on biologics.

So I think, Mr. Chairman, as we look at this, I would go back to Mr. Banwart's very strong emphasis on let's empower the FDA to do what we want the FDA to do. I think there has been significant concern by this committee and the Congress over the last several years about some of the problems at the FDA, some of the inadequate authority that the FDA has, some of the morale problems as well. So to me, this goes to a central issue here as to how we empower the FDA to do the job we expect it to do in order to remain the Gold Standard globally, when it comes to drug and biologic approvals and marketing.

I also would like to say that our piece of legislation is intended to catalyze this conversation. What we are interested in is moving in a thorough and very careful way but expeditiously because the amount of money that is being spent is just extraordinary and I appreciate Mr. Banwart coming forward because with biologic products alone, costs, as I understand it, have increased 45 percent in 3 years. We all know we've got to do a lot to get costs under control in our healthcare system. This is an area that—if we don't address everything else we want to do in healthcare—will not be sufficient because we will not be able to keep up.

So I very much appreciate the thoughtful testimony today, Mr. Chairman and look forward to working with our colleagues on both sides of the aisle and frankly, with the industry—both the innovator industry, the brand name industry as well as the generics and the biotech industry because what we're trying to do is in the best interests of safety, science, patient health and the cost of healthcare. I think that is the bottom line for all of us. So I appreciate it. We'll have some follow-up written questions because of the complexity of some of these concerns. But thank you again for testifying and thank our witness from the EU because it's wonderful to have cooperative, friendly relations with our neighbors across the Atlantic. So, thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Senator Hatch.

Senator HATCH. Well, thank you, Mr. Chairman. I want to thank each of you for being here. Mr. Rossignol, for you to take this time from Europe. It means a lot to us.

In all honesty, let me just start with you, Mr. Banwart. I understand how important it is to have low-cost healthcare for employees and to try and keep the costs within reason and of course, that's

what Hatch-Waxman was really designed to do in a lot of ways, plus a lot of other things that we designed in that particular bill.

While I admire Congressman Henry Waxman and Senator Clinton's work on this bill, I can't support it because I don't think it does provide the safety that we should have. Frankly, the safety provisions that we wrote into the original Hatch-Waxman bill back in 1984, indicated that we were deeply concerned about patient safety. I'm not convinced that if a follow-on biologic is approved the way that Congressman Waxman's bill dictates, patient safety, it seems to me, would be a problem because the legislation does not require any clinical trials on these products as they move through the pipeline. Now I would be interested, first in your thoughts, Mr. Banwart and then yours, Dr. Siegel and then yours, Dr. Hussain, on that particular issue. And if you could be short—I've got a number of other questions I really feel I have to get to.

Mr. BANWART. Thank you, Senator Hatch. Obviously safety is our number one concern as well and whatever process, whatever enabling legislation this committee would bring forward, we would assume that it would put safety at the top of the list.

Senator HATCH. This particular bill does not, in my opinion. It's innovative and very thoughtful and I think it's a good start. But you would agree that we should have clinical trials?

Mr. BANWART. We need to make sure that we empower the FDA to do the job safely.

Senator HATCH. Now, Dr. Siegel, I would appreciate your opinion in particular. I understand you have some ideas on how we might be able to reach biosimilar approaches.

Dr. SIEGEL. Well, in the interest of not taking up too much time because these are complicated questions, I'll be glad to answer in more detail and I've addressed some of these—

Senator HATCH. If you would, I would appreciate you getting with us and letting us know.

Dr. SIEGEL. I would simply say there are a lot of critical issues. The pharmacokinetics, whether a drug gives rise to an immune response, which most biologics do.

Senator HATCH. But you would agree clinical trials are improving?

Dr. SIEGEL. Absolutely. Both before and after approval, absolutely essential. It will depend on the nature of the product, how much and the nature of the disease and other factors but absolutely critical.

Senator HATCH. Well, thank you. Dr. Hussain?

Mr. HUSSAIN. Senator, I think we have the first approval from Europe as well as from the United States on this and I think clinical trials are part of the compatibility exercise and I think are often necessary. I don't see the interpretation of the proposed bill as not requiring clinical trials. So I don't envision that this will proceed without clinical trials. But I do want to sort of share with you a perspective that there are different aspects and different study designs that allow you to bring a rationale and a very designed approach to what clinical trials would be needed. So these are not exactly the same clinical trials you would have for the unknown original trial.

Senator HATCH. Mr. Rossignol—is it Dr. Rossignol or Mr. Rossignol?

Mr. ROSSIGNOL. Mr. Rossignol.

Senator HATCH. Okay. Now as I understand it, your basic provisions took effect in 2003 on biosimilars and that includes 10 to 11 years of protection against follow-on products. There is a combination of primary and secondary legislation and you use a guidance system to be able to make sure that these products are safe and efficacious, to use your terms and ours as well. As I understand it, the guidance will be issued through open public procedures with participation by expert committees, national authority, scientific community and industry approaches as well, which I find to be very, very interesting. I don't know quite how you put it together. I'd like you to write to us and let us know how you accomplish that goal. With product specific requirements established, pre-clinical and clinical testing required for all products, how—I hope I'm summarizing it well enough and special attention to immunogenicity and post-marketing testing and surveillance. Is that fair? Is that a fair description so far? And then I want to ask you these questions. I want to ask you some questions on that. If this is fair, tell me if it isn't, tell me as well. But could you please explain how substitution for medicinal products work in France. Are other EU countries following similar practices? And why isn't substitution appropriate for biosimilar medicines? If you could answer those four questions, that would be helpful.

Mr. ROSSIGNOL. First I have a concern that your description of the EU system is indeed the correct one. I would simply add in relation also to the comment made by Senator Clinton, that in Europe we have the legal basis for post-authorization safety studies and actually the Vice President of the Commission announced last week that this will be strengthened further in Europe to make sure that all products are safe and even post-authorization, post-marketing.

It is true that in Europe we have a system based on watching legislation which is relatively concise and flexible and supplemented, if you like, by guidance. I believe it is quite helpful to have this system in place. Why? Simply because this is an emerging field with respect to those products you're talking about and therefore it is very difficult to have one—monolithic if you like—system to address all these types of problems.

We do require clinical trials, pre-approval. We do require a comparable exercise, which is not restricted to clinical studies. It actually spans across the quality aspects, the pre-clinical aspects and the clinical aspects. So the comparability package is actually quite an extensive one.

I have to say also that in response to your last question on substitution, to be very concise. As I said in my statement, substitution or interchangeability is not assessed value in this station, so it is really a member state practice in Europe and it differs from one country to the other. So it's very difficult to give you an answer here. But I want to stress that today, we have examples of substitution, i.e., practice pharmacies for one product instead of the other, which are two products which are actually another two products. So in other words, what I'm trying to say is that the substi-



tution problem—interchangeability problem is maybe specifically applying—policy, when it is actually not specific to biosimilars. The problem already occurs today with other products at least in Europe, in certain countries where pharmacies are actually instructed, in some countries to substitute and to use, for example, the internationally known proprietary name. You find out that the majority of—and change one product with another without necessarily having the scientific background behind it. So we need to bear in mind that this issue of substitution is a key issue in the field of biotech products in general.

Senator HATCH. I want to thank you, Mr. Rossignol. Mr. Chairman, I think one of the big issues where we really could use help and I understand that you two doctors can help us with this—is just how we can really provide an element of protection here and without making the process so stringent that we can never get any products approved. We really need some help up here because we all know that it's almost impossible to have biologic implications—these are large molecule individual therapy-type situations. But that's where the future is, and we want to be helpful and have a similar drug price competition patent term restoration, which is the real name of Hatch-Waxman, approach towards these problems. And we could really use some extra help and from scientists all over the country. We would appreciate hearing from you on the best way of doing this and providing the most efficacious and safe way of doing it as well.

Thank you, Mr. Chairman for giving me that extra time.

Mr. HUSSAIN. Mr. Chairman, if I could just—sorry. You want to go first?

Mr. BANWART. Go ahead.

Mr. HUSSAIN. Mr. Chairman and Senator, this has been a significant talk process. Personally—I'll speak on my personal scientific aspect in this instance. I was personally not very comfortable with the generic substitution type of approach for follow-on proteins and the word follow-on was deliberately chosen to sort of illustrate some of the challenges here. But at the same time, I think in practice, you can achieve interchangeability through a science-based assessment in either one step or in a two-step processes that could be labeled as indications that this product has shown to be substituted—interchangeable to this and that is the reason I use the word interchangeable to distinguish from substitution. So label indication could be a mechanism to really—that is based on hard scientific data and even switching clinical studies that you might want to provide. If there is a risk-based approach that says the immunogenicity aspect of this is so critical, then there might be a two-step process that you might not get an interchangeability status unless you have additional post-marketing data that you collect because you really cannot do a clinical study. So that is a way forward here, in sort of my opinion and I think both my former FDA colleagues have been thinking about that for a long time.

Dr. SIEGEL. On the question of substitution, I think the only scientifically valid way forward is through some combination of naming, labeling and education to ensure that inadvertent substitution doesn't occur, to ensure that people realize that these products are not identical or the same. One cannot know that they are the same.

To look at say, a major safety risk that could be due to a trace contaminant—it would take tens of thousands of people studied to tell if that risk went from 1 to 2 percent, a doubling of the risk. If you look at immunogenicity concerns, which are big concerns, many of these products have immunogenicity in 5 or 10 percent of the patients. You could do a study of 500 to 1,000 patients and still not know if immunogenicity had doubled with the new product and exposing a patient alternatively, to one or both, could be exposing them to double the risk or could create immunogenicity risks that neither one alone exposure would bring around. So I think the science is a long way from addressing substitution but if your question is more broadly about a path forward to have abbreviated applications with abbreviated testing, I firmly do believe that with products that are sufficiently close in terms of their chemical, physical characteristics, that with appropriate testing, including clinical testing, that there can be a science-driven and product specific abbreviated testing approach to an abbreviated application.

Senator HATCH. Mr. Chairman, my time is up but on this particular point, could I have a follow-up question—since he's really gone into some immunogenicity problem. And I think it is really important. I appreciate your remarks about the problem of immunogenicity or the ability of most or all biologic products to stimulate an immune system response in the body but is it not true, just for our benefit here, since we're not scientists—we're just trying to do the best we can with your help—is it not true that an immune system response could occur immediately or it might not occur until years after patients start using a follow-on biologic. Is that true?

Dr. SIEGEL. Typically, immune responses will occur some weeks or months after somebody is first exposed to a new protein.

Senator HATCH. It can occur years later, too.

Dr. SIEGEL. Yes, it can, especially if there is a change in the product that they are exposed to.

Senator HATCH. Well then, don't you think that FDA should be given the authority to track some of these patients? Or at least have companies track patients in these clinical trials and allow the FDA to determine which follow-on biologics should be tracked in the future?

Dr. SIEGEL. I think that's essential. I think we're already seeing in some parts of the world where adverse events occur and you cannot determine which product the patient took and it's difficult or impossible to know whether those events, immunogenicity or otherwise, which products are attributable to. You can lose the value of a whole class of products if you can't tell which of its members are potentially problematic.

Senator HATCH. Well, this has been very helpful to us here today, the three of you have been very helpful and I have a number of other questions I'll submit in writing. Mr. Chairman, I apologize for taking a little longer than I should have.

Mr. HUSSAIN. Mr. Chairman, if I could just give my aspect, if I may. Immunogenicity is not just a protein issue. It also happens with small molecules and I think we really need a rational science-based discussion on this and I think the best place to do that is at FDA.

Senator CLINTON. Mr. Chairman, if I could just have a point of clarification? I appreciate greatly the line of questioning that Senator Hatch puts forth and I don't think there is anybody in the Congress who has more expertise on this. Our legislation provides the FDA with the authority to require clinical testing. That is in our legislation. So that some of the issues that we were talking about were based on the assertion that we did not do so and in fact, our legislation does give the FDA the authority and what we are trying to do is enhance the FDA's authority to deal with this whole range of issues. There is a differentiation between the post-marketing and the pre-approval and with respect to post-marketing, I agree completely with what Senator Hatch said. We should have follow-on testing by the companies and I think that should apply to both brand name and generics, both with drugs and with biologics because I think we're in a world now that is very different, even from the days of Hatch-Waxman, to try to figure out how we best can understand the complexity, the drug and biologic interactions, the immunoeffects. So I just wanted to clarify that our legislation does provide that authority to the FDA.

Senator HATCH. Well, if I could just clarify—it's not clear but I'm sure that's what you intend. What we need to do is keep working to get the very best legislation we possibly can. I'm sure under the leadership of the Chairman, we'll be able to do that.

Senator CLINTON. Yes. Well, we would love to have another Hatch-Waxman or Waxman-Hatch, whichever you prefer.

Senator HATCH. I want Clinton in there, too.

[Laughter.]

Senator HATCH. I want our Chairman and Vice Chairman in as well.

The CHAIRMAN. We have, if Senator Reed would permit, Senator Coburn told me that he has to go to an important Intelligence briefing in just a few minutes. So if I could recognize Senator Coburn.

Senator COBURN. You know, one of the things I think—just to kind of summarize, my reading of the testimonies. We're dealing with a completely different set of compounds than the FDA has ever dealt with before. And when you say biologic, you can talk about a very small protein. You can talk about a complex protein that has carbohydrates associated with it or you can talk about very giant chemical molecules. What I hear being discussed in both my readings and from talking to people, is I think the approach of this—and we don't know where we're going on this yet—is we're trying to write a law or to devise regulations based on where we don't want to go. I would suggest to the members of this committee is that what we ought to do is try to devise a stepped process based on what the FDA is going to learn and what we're going to learn in science. I'm not going to get into the battles of follow-on testing and clinical trials and everything else. I think a lot of that has to do with IP protection, investments in this, and appropriate competition.

But the question I have is when we don't know answers to questions, the one thing we want to make sure we do with our legislation is to make sure we don't impede an opportunity for greater development and faster responses to new products coming to the mar-

ket. We don't want to totally impede somebody's investment effort and IP and then take it away—so there has to be some protection for that. But at the same time, we ought to create a system where some of the intellectual property isn't taking advantage of the American people to the extent it is.

I think with the Clinton-Schumer bill, we ought to design provisional changes, step-by-step changes that allow the FDA to look at this and categorize this. We're not going to need the same law for all biologics. I think we need a different law for different groups of biologics, and I don't think we can know right now what that is. I'd love to have each of your comments on that. I think you're kind of seeing that's where the EU is going as well. Any comments on that?

Dr. SIEGEL. First let me say, I would agree entirely that there are things we can do with small molecules, for example, in terms of understanding the differences and making those differences so small that we can infer certain things about one based on its similarity to another that you can't do, for example, with live viruses.

Biologics law, however, is pretty flexible in terms of allowing one to determine safety, purity and potency as appropriate for the situation. So I wouldn't say necessarily we need new law for viruses. For example, each year there is a different strain of influenza. Each year, there is a new influenza vaccine for that. They are appropriately tested but it would be inconceivable to do large-scale efficacy tests each year against that strain because you wouldn't have the data in time. So I'm simply saying—

Senator COBURN. My point is this—you can have very large proteins that could come through a very simple manufacturing process, in the future, which we don't have today, that could be very pure, very low in immunogenicity and we're going to apply a law now that we don't have for that and we're going to have to come back and change it and maybe in a very short period of time. So my point is, we don't know what we're going to need. So anything we do in this area ought to have tremendous flexibility to build in what the science is going to show us in the future and I will bet you right now, I'm right. You will have complex molecules that you will produce very simply and with very low immunogenicity in the future and where a lot of these questions as far as interchangeability won't even apply. And yet we're making all our decisions today on the basis of what we know today, not what we think may come about in the future. So that was my point.

Dr. SIEGEL. Well let me just then say, I certainly agree that we should be careful to leave scientific discretion to the agency because each product is different because the science changes. But to Senator Clinton's point, I do want to say that yes, there is not any question that this bill authorizes the agency to require testing but I would note, for example, that in the approval of new drugs and biologics, the bill doesn't simply authorize the agency to approve clinical testing. It states there needs to be adequate and well controlled tests. It sets the floor—that floor is dictated by science and the presence in legislation of that floor gives guidance to industry, which is useful, gives guidance to the agency, which is useful, gives guidance to court systems, which is useful. There is a scientific basis for a floor here. That's the point I'm making.

Senator COBURN. Thank you, Mr. Chairman.

Mr. HUSSAIN. Senator, I think you raise an important point and I think legislation should really look forward and be set in a way that allows innovation and then new technology, science to really move quickly. But I think that the question I'm struggling with, the thing of this discussion is, I think we are specifically focused on follow-on. So these are products based on science and technology that are here now. So I think there is an aspect of the follow-on part for that and there is an aspect of getting more and more innovative medicines together. So I think there are aspects built into the proposed legislation which actually goes in that direction, like the second generation products, which European biosimilars regulations do not address. I think that's an important point and I really applaud that sort of thinking, to promote science and innovation with industry.

Senator COBURN. Thank you. Thank you, Senator Reed.

The CHAIRMAN. Senator Reed.

Senator REED. Well, thanks very much Mr. Chairman and gentlemen, thank you for your testimony today. I'm just wondering and I'd like to ask all the panelists, how do drugs and biologics compare in terms of intellectual property protection? Do these differences have any significance as we consider creating a pathway to approval of follow-on biologics? That's a topic I don't think has been addressed.

Mr. BANWART. Thank you, Senator. Representing Caterpillar, we certainly appreciate protection of intellectual property and we respect and honor patents of others and we expect others to respect and honor our patents. So intellectual property protection is important but we believe that after an appropriate period, that the marketplace should be subject to competition and that's been well proven in other fields and while there are technical differences, we believe that a positive spirit and approach here could result in a workable solution as well.

Senator REED. Okay.

Dr. Siegel.

Dr. SIEGEL. I would encourage you to and would welcome having others with greater expertise in my company speak to this issue but I would note that there are important differences—small molecules, since they are easier to define exactly what they are and how patents protect that. Large molecules, because they are enormous by comparison, often thousands of fold and because patents are increasingly more limited in what they cover, it's relatively easy to engineer around those patents through minor changes to different parts of the product that can break that sort of IP protection and that really does need to be taken into account in any legislation.

Senator REED. Thank you.

Mr. HUSSAIN. Senator, I'll just share with you, I think, that in the Novartis Corporation position on this, I think strong intellectual property protection, including patents, trade secrets and confidential information is essential to promoting innovation that results in new therapies to treat patients. With respect to each follow-on response, developing their own independent data packages

and not relying on innovator's data, we believe this protection can be respected while also allowing the new product to proceed.

Senator REED. Thank you. Director Rossignol, do you have a comment?

Mr. ROSSIGNOL. Well, as I said, I think the EU experience is going to be very interesting from a scientific point of view and we actually already discussed that international level with WHO and our experience in science, i.e., a set of data basically, that we require to approve these products and that, I think, can be easily shared and discussed. When it comes to the protection of product rights regarding innovation, et cetera, I think at least from my personal perspective, it needs to be a bit careful in extrapolating the EU model because the EU model is—without offending anybody in Europe, is quite complex and it is not, let's say, fully optimized across all member states in Europe and therefore, yes, we have a harmonized system now for data to pursue the same things. We don't have what seems to be in the draft bill on market exclusivity for follow-on biologics that would be interchangeable. We don't have that market exclusivity and Europe is restricted to—but in general, I would simply say that our system is very specific to yours when it comes to rewarding innovation and striking the right balance between rewarding innovation and smoothening the access to a further dimension.

Senator REED. Well, thank you very much. I guess my conclusion from hearing the responses and maybe I want to test this again is that there are significant differences, at least, to suggest that we have to look carefully at not adopting the same regime for intellectual property protections that we have for drugs or for—is that a fair summary of the—

Dr. SIEGEL. I believe so, yes.

Mr. HUSSAIN. I think so, yes.

Senator REED. Thanks very much. Again, this is a field that I'm a novice at, I'll confess. But I might not be alone. Does such a thing as a generic vaccine presently exist and would a generic vaccine be possible if a pathway to approve follow-on biologics were to be created and what might be some of the safety implications of generic vaccines?

Mr. BANWART. I'll defer to my colleagues.

Senator REED. Thank you.

Dr. Siegel.

Dr. SIEGEL. Well, vaccines are regulated under the Public Health Service Act where there are no provisions for generics at the present time. But vaccines—you know, if biologics are a skyscraper to the starter house that small molecules are, then vaccines are megalopolises full of skyscrapers and stadiums and all sorts of other enormous buildings. I think recent history has shown us that for a lot of vaccines—you know, small pox vaccine, influenza vaccine that two vaccines that are the same virus can have very different effects and that's something that needs to be paid really close attention to.

Senator REED. Doctor.

Mr. HUSSAIN. I think I'll just reflect back on the FDA knowledge and since I think FDA has done a tremendous job in approving vaccines and actually using brand knowledge to define what the ap-

appropriate pathway should be for vaccines. I think there are wonderful examples in the history on that.

Senator REED. Thank you very much. I note that—

Senator CLINTON. Senator Allard is here.

Senator REED [continuing]. Is here and Senator Kennedy is not so I think, Senator Allard, you should probably ask some questions.

Senator ALLARD. Thank you. I'm trying to get so I understand what follow-on biologics are. It seems to me that if you have a vaccine, for example or if you have a medication that has a source, different sources, I think sometimes the source and how that is collected and everything is as important as what the chemical make-up is. We have some products, I think that are extracted for animals. I think a pituitary extract, comes from animals and it seems to me that—I don't know how on follow-on biologics—if you're dealing with a pituitary extract—I mean, how can you assure safety? I think a source and how it's handled from that very source is as important as anything on that extract. I wondered if you could comment on that.

Mr. HUSSAIN. Well, I think from two perspectives. One, I think—just reflecting back on the name follow-on protein products at FDA was—this was being discussed and they were very specific that this should be the common protein product and not address and get into that aspect of that.

Senator ALLARD. Okay.

Mr. HUSSAIN. So that—

Senator ALLARD. So you're excluding those kind of products?

Mr. HUSSAIN. No, I'm just sort of sharing with you the concern that you raise with respect to source material. It is important but at the same time, I think there are technologies and there are approaches to address those challenges and I think we actually have a wonderful example of that currently under review with the technology, the collaboration, the momentum on—so I think yes, there are aspects to that but I think there are ways to address that approach, too.

Senator ALLARD. Well, you know, on vaccines for example, I know a lot of technology is changing on vaccines. You've got to kill virus. You might have a lot of protein in it, hormone or whatever and then you've got a modified live virus and then you have these other modifications where you take just the immunogenic aspect of the bacteria or the virus, which is a purer form with less reaction. And how do you treat those with a follow—in terms of—what's a follow-on biologic for something like that? How do you define that?

Dr. SIEGEL. First, let me second that for many biologics, especially those that are not made by DMA technology but even those, the source is critically important as is the process because of the limitations of testing. All of those things need to be controlled. But what is critical is probably for the purposes we're discussing here is less whether it is used as a vaccine than—although that can be factor in terms—it certainly is a factor in terms of what testing is needed, but the nature of the product itself. So as you referred to, there are some component vaccines that are just a highly purified protein made by recombinant and DNA technology whose characterization is of the same order as some of the protein products that we're talking about that are therapeutics. Many vaccines, however,

are far more complex, are live organisms, killed organisms, whatever, where the issues of determined comparability would be far less readily addressable. Even in the simpler vaccines though, they present the same issues as therapeutics do, of possible differences and of course, often in the setting of being given to thousands or millions of healthy children. So that—how the product is used is also going to influence what the appropriate testing is.

Mr. HUSSAIN. I agree with that.

Senator ALLARD. Pardon? You agree with that, okay. Well I just think that this is—it is a complex issue. I think what—not having some biological training, I think it's hard for people to understand. I've had some biological training and this is kind of a new concept, follow-on biologics, so I'm trying to understand it myself on how you're going to apply it with the testing that we currently require and the safety required for consumption. Those of you that are here, do you think that's a possible regulatory regime that we can implement?

Mr. HUSSAIN. What I would suggest is, I think, as there is possibly an example, I think the legislation could sort of recognize that this could be possible. It may not be possible fully at this time but I think this is what I think the European system has explicitly not excluded that and at the same time, I think with that level of complexity, getting into cells and getting into viruses and getting into those, may change over time.

Senator ALLARD. Yes?

Dr. SIEGEL. Is your question specifically about viruses, vaccines? Or is it sort of general?

Senator ALLARD. Well, I mean, we've got a generic term—follow-on biologics.

Dr. SIEGEL. Right.

Senator ALLARD. And I think it kind of makes our discussion kind of complicated because there is a lot of things that follow in under that and I'm trying to figure out how you—

Dr. SIEGEL. I think and Johnson & Johnson thinks that we can move forward in a careful way with those products that we can characterize the best and understand the best and with appropriate testing, that there is a path forward, that there are some classes of products, there are some uses of products—whatever, that will present substantially more challenges, some of which with science does not yet allow a path for new approaches to regulation.

Senator ALLARD. Dr. Rossignol, did you want to comment on that question?

Mr. ROSSIGNOL. Yes, thank you. Just again to share the EU experience in this field, I think it was mentioned by Dr. Hussain that indeed, legally we do not exclude the possibility today to have follow-on biologics or biosimilars approved, even if they would be vaccines or even more complex products. So that's not really excluded but I have to say that today, we are realistically on scientific grounds, the approach is really applicable to products which can be fully characterized and also products which have a good track record of—and clinical expertise and clinical experience. And if you talk about generic vaccines, specifically, we don't have that in the pipeline and the current consensus is really that we would not see that unless under very exceptional circumstances, we would not see



these types of products as being approved as biosimilars in Europe. Actually, the products we have in the pipeline are relatively simple biologics which are still far—let's say relatively more complex than chemicals but you're talking here about insulin growth hormones—maybe globally the way heparin is but not really products like vaccines or more complex products.

Senator ALLARD. So we're talking—the follow-on biologics would be things—be hormones of various types, basically, is that what we're looking at?

Mr. ROSSIGNOL. No, not specifically. I have to stress, no product in theory is excluded. I'm just trying to describe the scientific consensus today and really, the scientific consensus today is that you can have an abbreviated data package only if you are able to fully characterize your product to the best extent you have, even the current analytical terms you have. And that is, for the moment at least, applicable only to those products which are relatively simply in molecular terms.

Senator ALLARD. My problem is that this is such a broad term. And how do we narrow it down to what we're talking about?

Dr. SIEGEL. I think you're on the right track. It's not just hormones but the products that Mr. Rossignol are speaking of, for example, have molecular weights of 15, 20,000 typically. A typical aspirin might be—I think it's under 200. A typical small molecule may be in a few hundred. Some biological proteins are well over 100,000. Antibodies typically are 150,000 or more and then you get into genes and cells and viruses that raise other orders of complexity. So what he is saying and what I'm saying as well is that there are areas where there is a lot more scientific basis for characterizing the product and for using similarity as part of a regulatory paradigm.

Senator ALLARD. Yes. I mean, like our human growth hormone is, I think, traditionally at least in this country, is produced with cell culture. Am I right? I think it is cell culture. I visited an operation in Argentina. They've got cows, cattle that they have genetically modified to produce human growth hormone in the milk and they are extracting it out of the milk. And so I guess the source of that, in my mind, creates potential problems and that's one of the points that I wanted to make. I think the source can be a real concern, even though you're dealing with the same chemical.

Dr. SIEGEL. Absolutely.

Mr. HUSSAIN. May I?

Senator ALLARD. Yes.

Mr. HUSSAIN. I think really the source is as critical and I think it does have to be addressed and it creates challenges to be addressed in different ways. But I think if you could consider from the progressive signs and technology, not only from the range of the source material, the characterization, the analytics, the manufacturing process but also consider the progress we are making in the science of understanding the biochemical—as well as understanding the mechanism for actions. It opens up a whole host of opportunities to design your clinical trials in different ways. FDA has a wonderful initiative called the Critical Path Initiative where they are looking at biomarkers and so forth. So if one looks at all the opportunities that are out there, you may have challenges in terms

of characterization but you have opportunities for better ways of defining safety and efficacy and so forth. So I think—I really believe you have an opportunity to really share this legislation that is open to the opportunities that we can bring to our patients.

Senator ALLARD. Thank you.

Senator CLINTON. Well, thank you very much and one thing I'm taking away from the hearing this morning is that there seems to be agreement that we can and should approach a pathway for follow-on biologics being very conscious of all of the difficulties that such a pathway presents.

I know that in some of the back and forth with Senator Hatch, we were talking about some of the markers on that pathway and we're speaking about the pre-approval clinical testing and I think Dr. Siegel said that he didn't think the legislation we've introduced has adequate safeguards for the pre-clinical approval testing. Is that a fair characterization of what you said, Dr. Siegel?

Dr. SIEGEL. I think one could better protect patients with legislation that made clear the need for clinical testing.

Senator CLINTON. So that's really—we agree that we have to have clinical testing and we obviously are looking for a way to make that part of the pathway. But I wanted to ask Dr. Hussain, who didn't have a chance to respond to Senator Hatch on this, how do you assess scientifically the provisions in the legislation with respect to potential safety issues and the clinical testing approval process?

Mr. HUSSAIN. Senator, I think from my perspective, aspects of comparability with the science-based includes aspects of clinical trials and so forth. So those are inherent in the proposed legislation. So that was my interpretation of that reading. Clearly I think there is possibly a need for a bit of a clarification because Dr. Siegel comes from CBER and I come from CDER and his office got moved into my office so that's how we have interacted. I think from the CDER perspective, a far more kinetic study, a pharmacokinetic study, a pharmacodynamic study is not called a clinical study whereas I think it is called a clinical study. So I think there are different types of clinical studies and different aspects of clinical testing so I think clearly what we're seeing is clinical assessment. There is the pharmacokinetic assessment or a pharmacodynamic assessment or a comparative clinical trial. I think which clinical trial is appropriate really depends on how well you have characterized the product and then determine what clinical trials uncertainty should be managed and what commitment would be necessary. So the best situation for that is FDA has the ability and for example, each applicant will provide the data that justifies what clinical pathway should be taken. So I think that flexibility needs to be there and I think nobody has said that there is no clinical trial. I think everybody is doing clinical trials.

Dr. SIEGEL. I would add, though—I don't think there is confusion around that term. Pharmacokinetic and pharmacodynamic testing—pharmacokinetic testing, at least, is going to be critical but I think not sufficient. One needs to look at immunogenicity, one needs to have some safety experience, one needs—and this will be most possible where there are good pharmacodynamic measures so

you can be sure that you have the same effects of the same drugs at the same dose, which is true for some biologics but not for all.

Senator CLINTON. Well, I want to thank again all of our witnesses. The record will remain open for 10 days. A number of our members who wanted to get here could not make it. I want to thank Director Rossignol for being with us today. You've been extremely helpful in explaining the European Union approach and I also appreciate the way you characterized the legal authority versus the scientific consensus because I think that is something important to keep in mind, that we need to give the FDA authority and we need to empower them with adequate resources to begin to design this pathway and obviously, not everything is going to be ready or should go down together. We're going to have be more discriminating but we should leave that to the scientists and to the structure that we try to establish.

So again, I want to thank all the witnesses and we look forward to a very useful collaboration as we try to deal with some of these difficult issues confronting us. Thank you very much. The hearing is adjourned.

[Additional material follows.]

## ADDITIONAL MATERIAL

### PREPARED STATEMENT OF AARP

AARP appreciates the opportunity to present its views on the issue of follow-on biologics. AARP has endorsed the Access to Life-Saving Medicine Act (S. 623) because we believe this legislation will create a much needed pathway for the approval of safe, comparable, and interchangeable versions of biologics. We call on Congress to pass the legislation this year.

The Drug Price Competition and Patent Restoration Act of 1984 (commonly known as Hatch-Waxman) provided for the approval of generic versions of brand name prescription drugs. As a result, today, generic prescription drugs save consumers and health care payers billions of dollars each year.<sup>1</sup> Further, research has shown that billions more could be saved annually if the use of existing generics were optimized.<sup>2</sup> Popularity of these lower cost alternatives continue to rise, to the point where approximately 56 percent of all prescriptions filled in the United States, more than one billion prescriptions every year, are lower cost generic prescription drugs.<sup>3</sup>

At the time Hatch-Waxman was enacted some critics claimed that the legislation would harm research and development of new prescription drugs and consumers would suffer because companies would no longer invest resources to find new cures. History has shown these critics wrong. The pharmaceutical industry hasn't suffered—it is now the fifth most profitable industry in the country.<sup>4</sup>

Hatch-Waxman created an abbreviated pathway for the approval of generic drug applications and consumer and health care payors benefited. Now Congress has the opportunity to pass the Access to Life-Saving Medicines Act, which gives the Food and Drug Administration (FDA) the authority to approve generic versions of biologics. Once this legislation has been enacted, consumers and health care payers can begin to see savings on these life-saving medications.

#### THE COST OF BIOLOGICS HURT CONSUMERS AND HEALTH CARE PAYORS

Biologics are used every day to treat diseases and conditions such as cancer, multiple sclerosis, anemia, and rheumatoid arthritis. These treatment therapies are, in many cases, truly cutting edge technology. Use of biologic drugs is increasing every year.<sup>5</sup> Research and development into this vital field is growing—there are currently hundreds of applications in the pipeline. For example, for someone with rheumatoid arthritis it can make the difference between having the ability to walk and having to live with debilitating constant pain.

While biologics hold great promise for treating some of the most serious diseases, these treatment regimens can be very expensive. Some treatments can cost tens of thousands of dollars per month or hundreds of thousands of dollars per year. For example, Epogen, a drug used to treat anemia, can cost as much as \$10,000 per year. Cerezyme, used to treat Gaucher disease, can cost as much as \$200,000 per year—which is almost as much as the average price of a home in January 2007.<sup>6</sup> Similarly, a person diagnosed with colon cancer may have to use Avastin, which can cost \$100,000 per year, which is more than the average cost of a 4-year college education.<sup>7</sup>

Some individuals are fortunate enough to have insurance and the means to be able to afford these medications. However many are not so lucky. For example, a few of the choices for an individual managing rheumatoid arthritis are biologics such as Embrel, Remicade, and Humira. These drugs are among the top 20 largest sales in the biologics industry. For an individual with no access to prescription drug

<sup>1</sup> CBO, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.

<sup>2</sup> Emily Cox, Andy Behm, and Doug Mager, "2005 Generic Drug Usage Report," Express Scripts, June 2006. Available online at <http://www.express-scripts.com/ourcompany/news/outcomesresearch/onlinepublications/study/genericDrugUsageReport2005.pdf>.

<sup>3</sup> Statistics from the Generic Pharmaceutical Association (Available online at: <http://www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm>).

<sup>4</sup> Fortune 500 2006, "Most Profitable Industries: Return on Revenue," April 17, 2006.

<sup>5</sup> *Biotech Drugs Come of Age; Policymakers Take Note*, Health Affairs, Sept./Oct. 2006 (reporting that in 2005 revenues for biological drugs totaled \$50.7 billion, an increase of 15.8 percent over 2004).

<sup>6</sup> National Association of Realtors data, available at <http://www.realtor.org/research/index.html> (reporting the existing home median price was \$210,000 in January 2007).

<sup>7</sup> College Board, *Trends in College Pricing 2006*, available at <http://www.collegeboard.com/proddownloads/press/cost06/trendscollegepricing06.pdf> (reporting that average total tuition and fees at a 4-year private college or university for the 2006–2007 academic year was \$22,218).

coverage, they could choose between Embrel at \$1,384.42 per month, Remicade at \$598.97 per use, and Humira at \$2,831.76 per month.<sup>8</sup>

The astronomical cost of these drugs not only impact consumers, but also health care payers, such as employers, private health care plans, and public programs such as Medicare and Medicaid. Indeed, spending on biologic drugs continues to outpace even that of traditional brand name prescription drugs,<sup>9</sup> whose cost increases—at twice the level of inflation—are also too high.<sup>10</sup> For instance, according to a recent study commissioned by the Pharmaceutical Care Management Association (PCMA), approximately 30 percent of Medicare’s Part B prescription drug spending is for only five biologic drugs.<sup>11</sup> Sales for existing biologics continue to rise.<sup>12</sup> One way to control these costs is to provide a pathway for the approval of generic versions of these products.

#### LEGISLATION ENSURES SAFETY AND ACCESS

When brand name prescription drugs go off patent, a generic manufacturer can begin marketing its lower cost alternative after being approved by the FDA. However, no such pathway currently exists for biologics. Once these drugs go off patent, the manufacturers continue to reap the rewards of their patent long after its expiration and consumers continue to pay high prices.

Although biologics are more complex than prescription drugs, this complexity is not a valid reason for preventing the development of generic versions. Technology has progressed to the point where biologics are better understood and characterized. As a result, it is now possible to create generic versions of these treatment therapies.

The Access to Life-Saving Medicines Act grants FDA the authority to create a pathway for the generic approval of biologics. The legislation does not mandate that the FDA approve a certain number of applications—only that FDA provide for the pathway of approval. And the legislation leaves the scientific determinations up to those who are best equipped to address them.

As the science advances, we can continue to expect prescription drugs to become an increasingly important component of health care, and for biologic drugs to become a larger component of drug spending. It is critical not only for individuals, but for all health payers—including Federal and State governments, employers and insurers—that we begin to take steps to lower the cost of these drugs. Use of generic alternatives is an important element towards the goal of holding down health care spending over time. Creating an FDA pathway to generic alternatives for biologics has become a necessary part of the equation as well.

#### CONCLUSION

The Access to Life-Saving Medicines Act provides FDA the authority to produce a safe, comparable or interchangeable version of a biologic. The Hatch-Waxman Act created a similar pathway for prescription drugs. Twenty-three years later, the time has come for generic approval of biologics. Our members, and all Americans, need Congress to enact this bi-partisan legislation this year. We are pleased to see this committee and Members from both Houses of Congress and both sides of the aisle moving forward on this issue.

#### PREPARED STATEMENT OF THE COALITION OF STATE RHEUMATOLOGY ORGANIZATIONS

##### BIOLOGIC AGENT GENERICS (“BIO-SIMILARS”)

The Coalition of State Rheumatology Organizations is a national organization composed of 26 State and regional professional rheumatology societies formed in order to advocate for excellence in rheumatologic care and to ensure access to the

<sup>8</sup> Sales figures obtained from Lamerie Business Intelligence.

<sup>9</sup> Elise Wang, et al., *A Global “Generic Biologics” Guidebook*, Citigroup, Nov. 6, 2006, pg. 30.

<sup>10</sup> David J. Gross, Leigh Gross Purvis, and Stephen W. Schondelmeyer, *Trends in Manufacturer Prices of Brand Name Prescription Drugs Used by Older Americans, 2006 Year-End Update*, AARP Public Policy Institute Data Digest #DD154 (Washington, DC: AARP), March 2007 (finding that on average, pharmaceutical manufacturer prices for the 193 brand name drugs most widely used by older Americans rose at nearly twice the rate of general inflation in 2006).

<sup>11</sup> PCMA, *Potential Savings That Might Be Realized by the Medicare Program from the Enactment of Legislation such as the Access to Life-Saving Medicines Act (H.R. 6257/S. 4016) That Establishes a New cBLA Pathway for Follow-on Biologics*, available at <http://www.therightprescription.org/learn/rx-resources.html>, page 7.

<sup>12</sup> In 1999 the global pharmaceutical market was approximately \$331 billion, of which biologics represented less than 3 percent. In 2005, total pharmaceutical sales were roughly \$602 billion, of which biologics represented 7.6 percent. *Id.* at 4.

highest quality care for patients with rheumatologic and musculoskeletal disease. Rheumatologists are entrusted with the safe care of patients with rheumatoid arthritis and other autoimmune diseases that require the careful choice of safe and effective medications.

Rheumatologists are keenly aware of the dramatic long-term, life changing clinical improvements that biological agents have on some of the most crippling and disabling conditions that affect Americans. These biologic response modifying agents are available for the treatment of rheumatoid arthritis and other autoimmune diseases and have a significant impact on improving our patients' quality of life, preventing disability, decreasing morbidity and lowering mortality.

We are writing regarding H.R. 1038/S. 623 known as the Access to Life-Savings Medicine Act introduced by Senator Schumer, Senator Clinton, Congressman Waxman and others. This act attempts to establish a process by which the FDA will allow approval of lower cost copies ("follow-ons") of biological treatments in the United States. We are particularly concerned with language in this legislation that would allow ". . . data demonstrating that the biologic product is *COMPARABLE* to the reference product" and allows ". . . data demonstrating that the biologic product and reference product contain *SIMILAR* principal molecular structural features notwithstanding *MINOR DIFFERENCES* in heterogeneity profile, impurities or degradation patterns." We are concerned that this language does not recognize the unique complexities and difficulties inherent in the production of these biological medicines and the potential immunologic consequences of untested biologic agents that are not entirely similar.

These powerful agents have significant effects on the body's homeostatic immune function and can themselves be antigenic (can cause an immune response unique to the specific and unique structure). The immune response may vary with only minor differences between two very similar molecules. Even minor differences can cause a dramatic change in a molecules' secondary and tertiary structure resulting in a protein with vastly different immune mediated reactions. Each patient's response is unique and immune system dependent. These facts need to be considered in the approval process for generic biologic agents that are composed of complex proteins. There may be differences in effectiveness and a differential propensity to adverse reactions with even the subtlest alterations in primary, secondary or tertiary molecular structure. Adverse effects can include immunologic reactions to the medication, as well as potential long-term effects on the patient's ability to fight infection and ability to maintain malignancy surveillance.

The biologic protein molecules are produced by very complex manufacturing processes involving genetic engineering and living cell cultures that are currently required to meet precise and fastidious quality standards. Because of their protein nature, these agents are immunogenic requiring purity and consistency without a great degree of heterogeneity. Rheumatologists are just as familiar with the use of generic medications as other medical specialists. Generic medications are produced by organic chemistry processes and are currently required to comply with FDA reviewed efficacy and safety standards before marketing. The complexity of biologic medications and their effects demands that these standards are ever more important to maintain.

We recognize that follow-on biologic products are a natural evolution of biotechnology and we welcome the introduction of these medications. However, we must insist that safety standards of these drugs be even more rigorous than those for standard oral small molecule medications. There must be a scientifically based and logical application of an open and rational review process in order to assure the safety of our patients while generating the greatest possible benefit.

Unfortunately, the proposed legislation short-circuits the rational scientific process already in place and creates major concerns regarding safety and potential for immunogenic reactions as well as decreased efficacy. Abrogating the normal regulatory process that functions as a protective patient barrier will put all patients at risk of decreased efficacy, decreased quality and decreased safety.

The development and use of biological response modifiers in the rheumatologic therapeutics is relatively young. Significant unknowns and issues remain in using agents affecting the immune system. The current legislation could have unintended consequences with resultant increased patient risk. A process for evaluation of follow-on biologics should not deem minor the significant potential clinical problems related to increased heterogeneity, impurities, degradation patterns, amino acid sequences and immunogenicity related to secondary and tertiary molecular structure in the realm of "comparable biologics." These agents must be subject to careful scrutiny and scientific investigation before approval. A responsible regulatory process needs to examine all of the structural and functional features of the protein product with particular emphasis on differences relative to those currently manufactured

and currently approved. Product safety must be comprehensively examined before exposing patients to these very powerful immunologic agents.

Several examples of problems currently exist that illustrate potential problems. Products have been withdrawn from the market due to subtle differences in protein structure such as L-tryptophan, thrombopoetin and colony stimulating factors. Pure red blood cell aplasia has been linked to an erythropoietin “biosimilar” medication after it was introduced in over 90 countries. One case occurred in every 5,000 patients exposed and required a great deal of investigation before the cause was ultimately defined. In rheumatology, we have seen a variety of patient adverse reactions to the three different TNF alpha blockers currently available. There can also be significant differences in individual clinical responsiveness to one anti TNF agent as opposed to another.

Sponsors of the current legislation point to the European Union as having established a regulatory pathway for the approval of follow-on biologics. However, the regulations instituted by the European Medicines Evaluation Agency (EMA) are proceeding with a clear, proper and cautious regard for patient safety and we applaud this approach.

We welcome the introduction of a responsible regulatory process for the development of safe follow-on biologics. We support their development, as it will improve the access to care for more patients with most serious rheumatic diseases. However, this pathway must assure the safety and efficacy of these agents before their widespread or even limited use. We would be more than happy to work with you or participate in the development of a logical, open and rational process.

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INTERAMERICAN COLLEGE OF PHYSICIANS & SURGEONS,  
WASHINGTON, DC. 20006,  
*February 20, 2007.*

DEAR CONGRESSMAN: The Interamerican College of Physicians and Surgeons was founded in 1979 to promote cooperation among U.S. Hispanic physicians and to advance their professional and educational needs. The ICPS reaches a vast majority of the Hispanic medical community in the United States and Puerto Rico—over 39,000 physicians—and a growing number of health professionals in Mexico, the Caribbean, Central and South American and Spain. The ICPS is the largest association of Hispanic physicians in the Nation.

The ICPS has serious concerns about the Waxman/Clinton “Access to Life-Savings Medicines Act” introduced on February 14, 2007. As physicians, we rely on the FDA gold standard to ensure the safety of the treatments we prescribe for our patients. This legislation ties FDA’s hands in being able to provide physicians and patients with assurance that “follow-on” biologic medicines have been tested in order for us to know the safety profile of these treatments. All patients are not the same, and minority populations do not always respond to treatments in the same manner as other patients. Without mandatory testing, we, as physicians would be putting our patients at risk. In this environment of heightened discussion of drug safety, this legislation is, in our estimation, all risk and no benefit.

We would welcome the opportunity to further discuss our concerns and work toward legislation which accomplishes safety and savings for all patients.

Thank you.

Sincerely,

RENE F. RODRIGUEZ,  
*President.*

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THE AMYOTROPHIC LATERAL SCLEROSIS ASSOCIATION,  
WASHINGTON, DC. 20004,  
*February 23, 2007.*

Hon. HENRY WAXMAN,  
*U.S. House of Representatives,  
Washington, DC. 20515.*

DEAR CHAIRMAN WAXMAN: The ALS Association appreciates your efforts to reduce the cost of biologics and to increase access to these potentially life-saving treatments. As you may know, biologics show great promise in the treatment of ALS, or Lou Gehrig’s disease, and we strongly believe that patients must have timely access to treatment options that can save lives and improve quality of life. However, we are concerned about the potential impact of the “Access to Life-Saving Medicine Act.” While we are in the process of evaluating the full implications of the legisla-

tion for people with ALS, we are strongly opposed to any effort that attempts to attach the legislation to the reauthorization of the Prescription Drug User Fee Act (PDUFA).

The ALS Association is the only national voluntary health organization dedicated solely to finding a treatment and cure for amyotrophic lateral sclerosis (ALS). More commonly known as Lou Gehrig's disease, ALS is a progressive neurodegenerative disease that erodes a person's ability to control muscle movement. As the disease advances, people lose the ability to walk, move their arms, talk and even breathe, yet their minds remain sharp; aware of the limitations ALS has imposed on their lives, but powerless to do anything about it. They become trapped inside a body they no longer can control.

There is no cure for ALS. In fact, it is fatal within an average of 2 to 5 years from the time of diagnosis. Moreover, there currently is only one drug available to treat the disease. Unfortunately, that drug, Rilutek, originally approved by the FDA in 1995 has shown only limited effects, prolonging life in some patients by just a few months.

The hopes of people with ALS—those living today and those yet to be diagnosed—are that medical science will develop and make available new treatments for the disease; treatments that will improve and save their lives. Advances in biotechnology and the development of biologics present the ALS community with new opportunities to bring treatments from the lab to the bedside. While reducing the cost of biologics and other drugs is an important goal, policymakers must be mindful of potential unintended consequences. As we continue our evaluation of the Access to Life-Saving Medicine Act, we will share with you our views on the legislation. In the meantime, we urge you and your colleagues not to include the legislation as part of the reauthorization of PDUFA.

It is absolutely critical that Congress act promptly to reauthorize PDUFA and provide the FDA with the resources it needs to facilitate the development and availability of treatments for diseases like ALS. We fear that attempts to add issues such as the Access to Life-Saving Medicine Act will only delay PDUFA reauthorization to the detriment of patients.

The ALS Association appreciates your attention to our concerns and for your previous strong support of our cause and your constituents living with ALS. We look forward to working with you and your staff on these and other issues as the 110th Congress moves forward.

Sincerely,

STEVE GIBSON,  
*Vice President,*  
*Government Relations and Public Affairs.*

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SOCIETY FOR WOMEN'S HEALTH RESEARCH,  
*March 2, 2007.*

Hon. HENRY WAXMAN,  
*House of Representatives,*  
*Washington, DC. 20515.*

DEAR MR. WAXMAN: On behalf of the Society for Women's Health Research, we are writing to you to express our thoughts and concerns regarding your recently introduced legislation H.R. 1038, "Access to Life-Saving Medicine Act." While we commend the legislation's intentions to increase access to and reduce biological medicine costs through encouraged development of "follow-on" biological drugs (also known as biotech drugs or biopharmaceuticals), we are concerned about patient safety and feel it is important that such products meet appropriate "equivalency" standards. Since biological products are considered unique and any slight difference from the original product could have significant consequences for different populations, the Society believes that additional clinical testing should be required where appropriate.

The Society for Women's Health Research is the Nation's only non-profit organization whose mission is to improve the health of all women through research, education and advocacy. Founded in 1990, the Society brought to national attention the need for the appropriate inclusion of women in major medical research studies and the need for more information about conditions affecting women disproportionately, predominately, or differently than men.

The Society has long advocated for increased funding for research on women's health and encourages the study of sex differences that may affect the prevention, diagnosis and treatment of disease. Differences between the sexes exist, and whether a person is male or female matters in the prevalence and severity of a broad



range of diseases, disorders, and conditions. It matters at every stage of life—from the very beginning to the very end. It matters at every level—from the single cell to the entire body.

Science has shown us that even small differences can have enormous impacts on different populations, such as women and minorities. Such differences will exist in biologic products and therefore, follow-on biologics. It is imperative that these differences be studied and known through clinical testing as it is the only means to assure the safety profile of each product.

The Society recommends greater discussion of these issues as well as consideration and open discussion on what determinations the Europeans made in establishing their requirements for follow-on biologics. Only through an open forum with the input from scientists, physicians and those of us who represent the concerns of patients can we appropriately address this important issue.

Sincerely,

PHYLLIS GREENBERGER,  
*President.*

MARTHA NOLAN,  
*Vice President of Public Policy.*

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BIOTECHNOLOGY INDUSTRY ORGANIZATION (BIO),  
WASHINGTON, DC.,  
*March 8, 2007.*

Hon. EDWARD M. KENNEDY,  
*Chairman,*  
*Committee on Health, Education, Labor, and Pensions,*  
*U.S. Senate,*  
*Washington, DC. 20510.*

Hon. MICHAEL B. ENZI,  
*Ranking Member,*  
*Committee on Health, Education, Labor, and Pensions,*  
*U.S. Senate,*  
*Washington, DC. 20510.*

DEAR CHAIRMAN KENNEDY AND RANKING MEMBER ENZI: The Biotechnology Industry Organization requests the submission of this letter to the record of your March 8, 2007 hearing, to highlight our concerns about pending legislation to establish a mechanism for FDA approval of so-called “comparable” biological products. In particular, we urge that the committee not rush to complete action on legislation in this area to meet a compressed deadline that does not allow Senators to give this important and complex topic the deliberative consideration it deserves.

The members of the Biotechnology Industry Organization work on the forefront of medical advancement, developing innovative biological products that have revolutionized the treatment of diseases, including cancer, heart disease, infections, arthritis, and multiple sclerosis. In order to ensure a future of continued innovation by the biotechnology industry, it is essential that your discussions on developing an approval process for follow-on biological products be driven by responsible science, with a focus on protecting patient safety and preserving incentives to innovate.

BIO agrees with and supports the written testimony provided by Dr. Jay Siegel, Group President of Research and Development for Biotechnology, Immunology, and Oncology for Johnson & Johnson—a member company of BIO. The safety issues alone raised by this testimony argue for careful, deliberate consideration of any follow-on biologics pathway by the Congress.

In addition to ensuring patient safety, any follow-on biologics pathway created by the Congress must preserve incentives for research and innovation by ensuring protections for intellectual property and providing data exclusivity for innovative therapies and cures.

Unfortunately, the Access to Life-Saving Medicines Act (S. 623), which proposes to create such a pathway, is deeply flawed in all three respects. As Dr. Siegel’s testimony powerfully explains, this bill would jeopardize patient safety in numerous ways.

Further, contrary to its title, the bill would eviscerate incentives to develop life-saving new medicines through its one-sided alteration of long-standing patent law in ways that favor follow-on biologics manufacturers, who would be able to restrict and infringe the intellectual property rights of various parties including innovative biotechnology companies. S. 623 also should be opposed for its lack of data exclu-

sivity for innovative biologics. Data exclusivity provisions have served as an incentive for innovation under Hatch-Waxman and are part of the European system for regulating “biosimilars” (i.e., follow-on biologics). The legislation contains no prohibition on the FDA approving a follow-on product relying on innovator data immediately following approval of the reference product. Devaluing property rights and the absence of data exclusivity disincentivizes the necessary investment for a strong, vibrant pioneer biologic industry, upon which any follow-on market wholly depends.

In addition, we urge Congress to consider action relating to establishing a statutory pathway for approving follow-on biologics independent of the reauthorization of the Prescription Drug User Fee Act (PDUFA). Before a framework for follow-on biologics can be established, Congress must carefully consider and resolve complex scientific, legal, and economic issues. Meanwhile, it is important that Congress complete the PDUFA reauthorization in a timely manner and as a top priority. Although PDUFA formally expires on September 30, 2007, reauthorization needs to occur earlier this year to avoid potential delays in review of innovative new medicines. Attaching follow-on biologics legislation to PDUFA would potentially jeopardize reauthorization of the user fee program to the detriment of patients waiting for new therapies, FDA’s internal scientific capabilities, and biomedical innovation.

BIO represents more than 1,100 biotechnology companies, academic institutions, State biotechnology centers and related organizations across the United States and 31 other nations. On behalf of our members, we appreciate your consideration of our views and look forward to a continuing dialogue on this important topic.

Sincerely,

JAMES C. GREENWOOD,  
*President and CEO.*

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RESPONSE TO QUESTIONS OF SENATORS KENNEDY, ENZI, BINGAMAN, AND BURR  
BY JAY P. SIEGEL, M.D.

QUESTIONS OF SENATOR KENNEDY

*Question 1.* Dr. Siegel, do you think it is possible for a manufacturer to present a data package that would justify FDA saying a follow-on product is interchangeable?

Answer 1. Given the limits of technology, it is not possible for a manufacturer to present a data package capable of scientifically justifying any claim or determination of a follow-on product to be interchangeable with its reference product. Laboratory testing has the potential, in some cases, to demonstrate a high degree of similarity. Such a demonstration could, in some cases, allow a determination of the safety and efficacy of a follow-on biologic based on a more limited clinical data set than would be required of an entirely novel molecule. I believe, however, there is no technically or practically feasible data package that could support a claim of interchangeability while ensuring patient safety.

Follow-on biologics are, by definition, different products, and the potential for clinically important differences from the reference product exist. As I testified, it would take testing in several thousands of patients to ensure that the serious adverse events rate had not doubled from 1 percent to 2 percent. Testing simply cannot establish that clinical effects will be identical; inadvertent switching of a patient doing well on one medication to a different, though similar medication will run the risk of an adverse change with regard to clinical response.

Even if the testing profiles of two products appeared essentially identical, inadvertent substitution pursuant to a designation of interchangeability could subject patients to additional risks. For example, if the risk of immunogenicity for patients exposed to a reference product is 5 percent, and for patients exposed to a follow-on biologic is also 5 percent, given the various factors that can lead to immunogenicity, the risk of immunogenicity in patients switched between the products could well be 10 percent, even if the two drugs were established to have equal efficacy profiles.

A designation of interchangeability for products with potential differences, and the resultant switching of patients, could significantly impair the ability of pharmacovigilance (i.e., drug safety and surveillance) systems to limit the risks associated with emerging safety problems. If an adverse event occurred, it could be difficult or impossible to determine which “interchangeable” product was responsible. This could both delay detection of a new problem and impair ability to correctly identify the source of the problem.

As with any other biologic with activities similar to those of another product, e.g., the various interferons alfa, antibodies to tumor necrosis factor, and erythropoietins,

follow-on biologics that have been found to be safe and effective should be administered only with the full knowledge and consent of the patient and the treating physician regarding which product is being given. Follow-on biologics policy should both limit the possibility of substitution without a physician's knowledge and support good pharmacovigilance through labeling and naming.

*Question 2.* Dr. Siegel, doesn't the FDA already make a finding of interchangeability every time it approves a manufacturing change? For instance, if a manufacturer were to change a cell line the FDA does not require that the manufacturer change the label or inform consumers that such a change has taken place.

*Answer 2.* Manufacturing changes for an existing product do not pose the same risks I discussed above with regard to interchangeability for follow-on biologics. There are two reasons this is the case:

- First, in the case of manufacturing changes, the risk of being unable to track which product is accountable for an adverse event and the risk of patients being exposed to additional dangers by being switched between two products are both minimized because there is a limited period in which the pre- and post-change product co-exist on the market. Indeed, in my experience, when there is a change that raises concerns about a possible change in profile, FDA will ask that the period of overlap in the market be minimized. In contrast, follow-on biologics would often co-exist in the market with the reference product and possibly other follow-ons for extended periods.

- Second, the extent of changes, and therefore the risks of undetectable but meaningful differences, with a follow-on biologic are quite high compared with those typical of a biologic undergoing a manufacturing change. The manufacture of a follow-on biologic will typically entail simultaneous, substantial changes to many key aspects of manufacturing—including changes in cell line, many aspects of the manufacturing process, and facility. While these changes are unavoidable for follow-on manufacturers, manufacturers of an approved product, understanding the risks of comparability determinations, are extremely cautious about attempting any of these changes and would be extremely ill-advised to propose multiple simultaneous changes this radical.

The risk of clinical differences inherent in such extensive changes is further substantially increased in the case of follow-on biologics since the follow-on manufacturer, unlike the innovator, has limited or no access to intermediaries and to the extensive knowledge of the product and its manufacturing process that make it possible for innovator companies to assess and avoid the risk of clinically important changes to their products.

Let me explain this point further: When a manufacturer of a biologic that has already been marketed and/or extensively studied, makes substantial changes in its manufacturing process, that manufacturer is able to compare not only final product but also various components and intermediates that are produced during various stages of both the new and old manufacturing process. For example, depending on the changes made, comparisons might be made of the unpurified biologic (made by the old and new processes), and/or of purified product prior to formulation. This testing is very important because it may detect the presence of new variants or contaminants that, after purification and/or formulation, may be reduced or masked such that they are still present but undetectable in final product.

Manufacturers of follow-on biologics will not have any of the components and intermediate materials for testing and will have access only to the final, marketed reference product.

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

Because the manufacture of a follow-on product will necessarily entail drastic changes to the process absent in-process materials, comparative testing capabilities and knowledge, it is inapposite to attempt to equate FDA standards for changes to the manufacture of an innovator product—as stringent as those standards are—with what can or should be the standards for follow-on biologics.

## QUESTIONS OF SENATOR ENZI

*Question 1.* The Intellectual Property provisions in the Clinton-Schumer bill have been described as unbalanced by some. Do you think this is a fair criticism? If this law was in place, how would it change your investments that you make in research and development?

Answer 1. As I stated in my testimony, it is critical that any pathway for follow-on biologics provide appropriate incentives for innovation so that the promise of new and innovative biologic therapies can continue to be realized for patients for generations to come.

In my current position as Group President of Research & Development for Biotechnology, Immunology and Oncology for the Johnson & Johnson Family of Companies, I experience first hand the issues presented by the enormous effort and investment it takes to bring a new biological entity to the market through the regulatory approval process. Only a small portion of potential drug candidates reach human trial phase and only a small portion of those drugs actually reach the market. And it has been demonstrated that well over \$1 billion in research and development is spent for each new drug brought to market (Source: Tufts Center for the Study of Drug Development Impact Report, Vol. 8, No. 6 November/December 2006).

Thus, the high cost of drug development and the uncertainty associated with the outcome of pre-clinical and clinical trials necessary for marketing approval makes investment in this area an extremely costly and risky business. While we are committed and dedicated to developing new therapies to address unmet medical needs, this risky and costly drug development can occur only when there is both a sound scientific case and a sound business case to support the programs.

In the face of this, S. 623 would provide a pathway for the abbreviated approval of follow-on biologics that relies heavily on the investment made by the innovator company, with no provisions to ensure that the innovator of a biological product will be able to recoup the enormous investment made before facing competition from follow-on manufacturers. Unlike the 1984 Hatch-Waxman Act, which sought to balance the goal of facilitating the rapid introduction of lower-cost generic drugs with the goal of promoting innovation in the pharmaceutical industry, S. 623 includes little or nothing to promote innovation in the industry.

It may be asserted that no such provisions protecting innovation are necessary because the innovator can rely on its patents to protect the product from competition for a sufficient period of time to recoup the investment and promote innovation. However, as we have seen from the patent litigation that has ensued as a result of the 1984 Hatch-Waxman Act, patents alone are an imperfect and highly uncertain system upon which to rely for market exclusivity for pharmaceuticals.

The ability to rely on patents for protection of innovation will be even more limited for biologics. The patent system governing the acquisition and enforceability of biological patents is generally moving towards the issuance of patents with increasingly narrow claims. Additionally, many biologics are imperfectly protected only by process patents that may be "designed-around" by an alteration of the process that avoids infringement. But proposed follow-on biologics legislation, including S. 623, will allow for approval of follow-on biologics that are "similar" but not "identical" to the innovator product. Particularly with the broad range of differences allowed under the definitions of "highly similar" in S. 623 (e.g., even allowing the follow-on biologic to have a different amino acid sequence of the product), there will be ample opportunities for follow-on biologics to "design-around" the typical patents protecting a biologic.

Thus, under a statutory scheme such as that outlined in S. 623, a follow-on version could be similar enough to an innovator product for the purposes of regulatory approval, but different enough to avoid patent infringement. The combined effect of these forces could reduce effective market protection for innovator products that, in turn, could stifle the environment for investment in the development of new biologic medicines. There is no doubt that this would impact development decisions.

While I do not claim to be an expert in pharmaceutical intellectual property litigation, experts in Johnson & Johnson inform me that S. 623 contains a number of provisions which would actually weaken the ability of innovators to enforce what patents they are able to obtain. For instance, the bill would restrict the innovator's ability to bring a patent infringement suit against an infringer unless they identify all of their patents in a timely manner, and then the suit may be brought only in the judicial district in which the infringer consents, thus depriving the innovator the ability to bring suit in the judicial forum of its choosing. Further, unlike the 1984 Hatch-Waxman Act, there is no stay of the regulatory approval of the follow-on biologic when a patent infringement suit is filed. Finally, if certain conditions are not met by the innovator, in some cases the innovator may only recover a "reasonable

royalty” in a patent infringement action, a provision which amounts to a compulsory license for the follow-on biologic; in other cases, the innovator is prevented from bringing an infringement suit at all.

We would be pleased to offer input as you consider the important question of incentives for innovation as you examine legislative approaches to follow-on biologics.

*Question 2.* Johnson & Johnson operates in Europe. Are you satisfied with the process that the Europeans have created to license follow-on products?

*Answer 2.* We are fortunate that the EU has already made substantial progress in developing and implementing a policy based on science and public health. While the United States should have a policy that is designed for our own regulatory, legal, and healthcare environment, there are many aspects of the EU process and policy that are admirable.

EU legislation clearly distinguished a “biosimilar” (the term they use for a follow-on biologic) from a “generic,” acknowledging the differences between products containing small synthetic molecules and those based on biotechnology-derived proteins produced by living cells. The quote below from the EMEA guideline on biosimilar products (CHMP/437/04) provides a good summary of the philosophy underlying the EMEA’s position on biosimilars (follow-on biologics).

“It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”

The EU legislation did not attempt to define the scientific standards for approval of biosimilars; it entrusted that task to the EMEA, the science-based body responsible for approving the marketing of drugs in the EU. The EMEA pursued a science-based, transparent and open process in which all parties were invited to offer input to establish concept papers and draft guidances, starting with basic principles for all biosimilars. This was followed by more specific guidances with testing requirements by product groups. The EU requirements allow for abbreviations in testing where science and safety permit, but clinical testing, immunogenicity testing, and post-marketing safety surveillance are recognized as important to minimize the risk to patients and are critical parts of the EU approach.

The European Union rightly acknowledged in its own process of developing a pathway for follow-on biologics that follow-ons can be similar, but never identical to an innovator biologic.

Specific legislation with regard to interchangeability has been left to Member States and several weeks ago (Feb. 18), the French parliament adopted legislation to prevent follow-on biologics from being treated in the same way as traditional generics and banned the automatic substitution of one biologic medicine for another.

Johnson & Johnson is pleased with, and participated in, the open and transparent process used in Europe to determine the testing standards for follow-on biologics that are truly highly similar to a reference product. We should be able to leverage that work to have a frank, transparent and scientific debate here in the United States, and thereby develop a model that will be compatible with our own regulatory and healthcare environment.

*Question 3.* If there is general agreement that an abbreviated pathway for biologics is appropriate, why shouldn’t we just modify the Clinton-Schumer bill to address the identified concerns instead of creating new legislation?

*Answer 3.* Johnson & Johnson fully supports efforts to identify a pathway for follow-on biologics. As I indicated in my testimony at the Senate HELP hearing on March 8, this pathway should be science-based, with paramount attention to patient safety and well-being. To that end, there are a number of principles critical to address in any abbreviated system for follow-on products. Four of these principles are: (1) There will always be a need for appropriate pre-marketing testing in humans to ensure that a follow-on biologic is safe and effective; (2) A follow-on product should be highly similar to its reference product and as similar as is achievable—there need not and should not be allowance for determinations of “comparability” for products that are unnecessarily different or so different in structure that they should be considered different products entirely; (3) A follow-on product should not be considered interchangeable with its reference product; (4) FDA must be fully empowered to require effective post-marketing safety surveillance, to seek commitments for post-marketing clinical studies, and to request data and studies in support of sound scientific decisions without constraints.

In addition to reflecting an overriding concern for patient safety and well-being, any legislation for follow-on biologics should ensure a science-based, open and transparent process allowing broad-based expert input into the establishment of testing standards. Importantly, it should also provide incentives for innovation so the promise of new and innovative biologic therapies can continue to be realized for patients.

The principles enumerated above, the need for incentives for innovation, and the establishment of an open and transparent process for the creation of testing standards should be critical elements of the foundation and starting place for any proposed legislation for follow-on biologic products. S. 623 is not based on these principles, provides no incentives for innovation, and does not encourage or even suggest an open process. Therefore, S. 623 should not be used as a starting place for follow-on biologic legislation.

#### QUESTIONS OF SENATOR BINGAMAN

*Question 1.* To address the issues around substitution of one biologic for another, how would you recommend that data be obtained in the post-market period to assure safety of both the innovator compound and the follow-on (or biosimilar)? Please discuss pros and cons of each potential stakeholder contributing to the data gathering process: manufacturer, third party payer, prescribing health professional, patient, regulatory agency.

Answer 1. Because a follow-on biologic cannot be established to be identical to the reference innovator product, interchangeability should not be permitted. This has been recognized in the European Union. Unless there are clinically important reasons for making a deliberate choice to substitute one biologic for another, substitution as we generally understand it should be avoided.

Appropriate pharmacovigilance (post-marketing safety surveillance) requires that the causative product for an adverse event be identifiable to the greatest extent possible. To achieve this end, patients and prescribing health professionals should be aware of precisely which biologic the patient is taking. Switching between therapies should be carried out only when there are clinically important reasons and with full knowledge of the patient and physician. Follow-on biologic policy should optimize the ability to identify the product actually received through approaches such as naming, labeling, and physician and patient education.

As part of reviewing the application for a follow-on biologic, just as for any other biologic, FDA should determine what studies should be performed in the post-marketing period to address outstanding questions. This determination will depend on the information provided about the molecule and its clinical effects in the application, upon knowledge about other molecules in the class, and upon a determination of what information should be required pre-marketing.

It is important to recognize that the prohibition in S. 623 against FDA requesting any post-marketing studies of the follow-on biologic other than those requested of the innovator is scientifically problematic. Data in the follow-on application (e.g., presence of a trace contaminant, weak signals of a possible toxicity based on lab findings, suboptimal clinical data addressing a safety concern) may point toward the importance of specific post-marketing studies for the follow-on product. Knowledge emerging since the approval of the innovator may raise key questions already addressed by years of experience with the innovator that need to be addressed for the follow-on biologic.

To ensure good pharmacovigilance for any biologic, patients should be encouraged to report possible adverse events to their healthcare provider and physicians should be encouraged to report appropriately to the FDA and manufacturer. In addition, all manufacturers should be required to have in place systems for the ongoing collection and evaluation of post-marketing data as a method for detecting risks across the product lifecycle. The specific range of programs for the collection of post-marketing data can range from prospective trials, epidemiologic studies, registries, or simply post-marketing surveillance.

*Question 2.* Can you propose a possible mechanism for communicating to stakeholders (above) during the process of post-market surveillance? Would different information go to different stakeholders at different times, or would all the information be equally accessible to all stakeholders?

Answer 2. Health care professionals and others who become aware of possible new safety concerns should report new safety information to the FDA and drug sponsors/manufacturers in a timely manner. In most cases, post-marketing safety information will not result in the need to urgently communicate new safety information, and in these cases, periodic reporting of specific data from surveillance programs and appropriate studies should occur in a timely fashion at a frequency agreed between the manufacturer and FDA prior to approval. This "raw" data should be sub-

ject to expert evaluation before further dissemination. Dissemination of such raw data to recipients not equipped to evaluate its significance and place it in context could inadvertently cause unwarranted concern or result in inappropriate cessation of life-saving or enhancing therapy.

After evaluation, new information that adds significantly to understanding the expected effects of a drug should be further distributed to all stakeholders, including patients. However, it is critical that information to patients be balanced and delivered in the context of the needs of and alternatives for the individual patient. This is typically best done by the informed health care professional.

#### QUESTIONS OF SENATOR BURR

*Question 1.* Do you support the Clinton-Schumer bill in its entirety?

Answer 1. As I indicated in my testimony at the Senate HELP hearing on March 8, Johnson & Johnson does not support S.623—not in its entirety and not as a starting place for follow-on biologics legislation. Any legislation for follow-on biologics should be based on well-grounded science, with paramount attention to patient safety and well-being. In addition to an overriding concern for patient safety, any legislation for follow-on biologics should provide incentives for innovation so that the promise of new and innovative biologic therapies can continue to be realized for patients for generations to come, and should encourage an open and transparent process to establish testing standards that ensure the safety and effectiveness for this new category of products. Unfortunately, S.623 does not reflect these principles.

What follows is a brief outline of areas I consider most problematic:

• **S.623 fails to provide important clarity pertaining to a requirement for pre-marketing clinical data to ensure that a follow-on biologic is safe and effective.**

- Extensive experience confirms that manufacturing differences such as those between the manufacturing processes for a reference innovator product and those for a follow-on biologic are likely to lead to differences in product safety or efficacy. Not infrequently, these will be detected best or only in clinical testing.
- As a rule, and as experience has made clear, clinical studies must be considered a necessary and mandatory part of properly evaluating any and all biologic products and should be a fundamental piece of any proposed regulatory pathway for the approval of follow-on biologics.
- FDA requires that innovators conduct clinical testing after major manufacturing changes before marketing product made by the new process. American consumers have been protected from major clinical risks to date as a result and will continue to be so protected only if follow-on biologics are required to undergo appropriate clinical testing.

• **S.623 allows for determinations of “comparability” for products that are so different in structure that they should be considered different products entirely.**

- There is no scientific basis for allowing abbreviated testing of a new biologic on the basis of it being only distantly related to an existing one. Some differences are so substantial that the biologics should be considered different products entirely.
- S.623 allows a molecule to be considered “to contain highly similar principal structural features” even if it contains “minor differences in amino acid sequence” or differences “due solely to post-translational modifications.” Differences in even just one amino acid and many types of differences due to post-translational modifications can have devastating effects on the function of a protein. Such differences scientifically define the product as a different product and provide no scientific basis for abbreviating the data requirements to demonstrate safety and efficacy.
- Due to the inability to make an identical biologic, follow-on policy will necessarily go beyond generics policy in allowing abbreviated testing for products whose active ingredients are highly similar (as opposed to equivalent as with generics). S.623 unnecessarily goes much further allowing abbreviated applications for products that are intentionally and/or avoidably different from a reference. There is no need justifying the risks incumbent in such a policy.
- S.623 would also allow “closely related, complex, partly definable biological products with similar therapeutic intent” (for example, two live viral products for the same indication) to be considered “highly similar.” This provision inap-

- appropriately allows abbreviated applications for living cells and organisms and other biologic products far more complex and difficult to define than proteins.
- Even after drawing extremely broad boundaries around what types of differences (and what types of products) would fall within the scope of comparability determinations and abbreviated applications, S. 623 undermines even those boundaries. It gives the Secretary leeway to determine any two biological products “to contain highly similar principal molecular structure” regardless of known or indeterminate differences. So in essence, S. 623 places no limit on the types of physical and chemical differences that might be considered minor enough to permit a demonstration of comparability and an abbreviated application.
  - Allowing products with avoidable structural differences from a reference to be deemed comparable is not only unnecessary (as the differences are avoidable), and risky (the presence of such differences leaves little or no basis for abbreviated testing), it also discourages innovation by allowing follow-ons to design around patents and undermine the incentives for innovation.
  - **S. 623 allows a follow-on product to receive a determination of interchangeability with its reference product, a scientifically unsound proposition that presents serious challenges to pharmacovigilance systems and patient safety.**
    - From the standpoints of science, clear communication, and public safety, interchangeability is not an appropriate designation for follow-on biologics.
    - Unfortunately, not only is interchangeability for follow-on biologics included in S. 623, the statutory test for interchangeability is completely open-ended. As written, this statutory test could be used to determine that two drugs are interchangeable even if they do not contain the same active ingredient. This is entirely at odds with the concept of “therapeutic equivalence” that has been applied to small molecule drugs and which requires a finding of the same active ingredient, same dosage form and dose, and bioequivalence.
    - If the designation of interchangeability leads to substantial numbers of patients switching between therapies, it could severely impair the ability of pharmacovigilance systems to deal with emerging safety problems. When a new adverse event emerges or a known one increases in frequency, it may be impossible to attribute the adverse event to a specific product if patients experiencing the event have received multiple products. This is especially the case for some types of adverse events, such as those due to immunogenicity, that tend to arise in patients well after receiving the causative product.
  - **S. 623 places limitations on FDA’s ability to require post-marketing studies that might be critical to ensuring safety, and is silent on post-marketing surveillance.**
    - Follow-on biologics will raise safety concerns—such as differences in immunogenicity profile or emergence of unexpected toxicities—that will require studies beyond the scope that pre-marketing studies can reasonably address.
    - S. 623 places specific limits on the FDA’s ability to request commitments for post-market clinical studies from a follow-on manufacturer. It specifically would not allow FDA to request studies specifically targeted to address residual concerns raised by the limited testing done by the follow-on biologic application.
    - In addition, S. 623 is silent on the matter of post-marketing safety surveillance, a tool essential to ensuring the safety of all biologics, including follow-on biologics or any pharmaceutical.
  - **S. 623 subjects the FDA to undue constraints in its ability to ensure safety and efficacy of follow-on biologics.**
    - As we enter this new field with new safety risks, the FDA should be unhampered in its ability to request and receive additional data from a manufacturer as the need becomes apparent. To do otherwise could jeopardize patient safety.
    - The bill provides that, when asked, the FDA should meet with follow-on sponsors to “reach agreement regarding the parameters of design and size of the studies” necessary for approval of the application. The binding nature of these agreements presents a troubling departure from requirements pertaining to new drugs and traditional generic drugs: Whereas binding agreements in those contexts are limited to pivotal studies (i.e., clinical trials and bioavailability and bioequivalence studies) and made after review of extensive preliminary data, here, the binding agreements are not so limited and could



be requested prior to generation of any data. The FDA cannot and should not be expected to identify all testing needs up front before early test results are available. Also, existing provisions apply to determinations FDA has made many times over many years (i.e., drug, biologic and generic approvals), so FDA has a vast experiential basis for determining what tests are required. By contrast, FDA has never made a comparability determination for a follow-on biologic such as proposed in S. 623. It is therefore unreasonable to require the FDA to anticipate all testing needs in advance and potentially dangerous to limit FDA ability to request additional data.

- Another worrisome constraint on the FDA comes in S. 623's mandate to the FDA to complete its final review and take final action on a follow-on biologic product application within just 8 months of the manufacturer's submission of the application. This would be an unprecedented move that places inappropriately high priority on the review of follow-on biologics: Most new drugs and biologics are reviewed with a 10-month deadline to complete review, potentially much longer to reach final action. Even priority drugs and biologics have a 6-month review, and potentially take much longer to final action. Also, timelines for new drugs and biologics address the time for a *complete review* of an application. After complete review, FDA may request any data not found in the application. In contrast to the approach for innovator products, S. 623 sets an aggressive timeline not for a complete review, but for a *final action*. At the end of the 10-months review period, the FDA is not allowed to request additional important data; it must make a final decision. Given complexities of a comparability determination and the potential associated risk, legislation should promote, not limit, requests for important data.
- S. 623 also specifies that studies to establish comparability should be designed "to avoid duplicative and unethical clinical testing." The meaning of "duplicative" is unclear; but whereas replication of results is a basic scientific approach to ensure validity, admonition to avoid duplicative testing, depending on how the term is interpreted, could lead to inadequate testing. Regarding unethical testing, the language is unnecessary and could, depending on how it is interpreted, discourage appropriate testing requirements.
- **S. 623 provides no data exclusivity provision for innovators and thus does not provide adequate incentive for exclusivity.**
- **S. 623 does not ensure an open and transparent process for setting scientific standards.**

*Question 2.* I am sorry to see that we do not have a witness testifying on the impact of the Clinton-Schumer bill on the financial viability of innovator biotech companies. If we did have such a witness, I think the witness would say that venture capital for biotech companies would dry up because this bill guts any drive for biotech companies to innovate. Why should a biotech company go through huge clinical trials, manufacturing challenges, studies, etc. to get a biologic approved when the day after approval a follow-on biologic company can send them a letter asking for a list of every single patent that is a part of making that biologic. And after providing that list, the innovator can only sit back and wait for the follow-on biologic company to submit an application at the FDA saying that their product is comparable to the innovator's product—not the same—but comparable. This bill has no data exclusivity for the innovator. There is no patent protection for the innovator. And there is no marketing exclusivity for the innovator. Why should venture capital firms invest in biotech companies if the companies have no guarantee of recouping their research investment? Dr. Segal, I would appreciate your comments on this concern.

*Answer 2.* The majority of biotechnology companies are small, privately held companies with no product revenue stream. Relatively few are currently profitable. These small companies have been the source of many innovative ideas and products. Raising sufficient venture capital is both a necessity and a great challenge for many of these small, innovative biotech companies.

A bill like S. 623 that provides no marketing exclusivity for the innovator and contains provisions that weaken patent protections could very well have the effect of driving away venture capital money upon which the small start-up companies in the industry depend. Of course, this would decrease the amount of research and development being done by the industry on innovative biotech therapies.

RESPONSE TO QUESTIONS OF SENATORS KENNEDY, ENZI, BINGAMAN, AND BURR  
BY NICOLAS ROSSIGNOL

QUESTIONS OF SENATOR KENNEDY

*Question 1.* Are EU requirements for clinical testing of follow-ons specified in statute or in regulation and guidance?

Answer 1. The EU legislation on “biosimilar” products (the EU equivalent of follow-on biologics) lays down that the type and amount of data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines. Requirements for clinical testing are specified in guidelines established by the European Medicines Agency (EMA) ([www.emea.europa.eu](http://www.emea.europa.eu)).

*Question 2.* Could you explain the function of product class guidelines in the European Union?

Answer 2. There are currently four “biosimilar” product-class guidelines in the EU, which address product-class-specific pre-clinical and clinical aspects on insulins, growth hormones, erythropoietins and granulocyte-colony stimulating factors. In addition, one on low-molecular weight heparins is also in preparation.

The purpose of EU product-class guidelines is to outline the general non-clinical and clinical requirements. The guidelines present the current view of the EMA on how comparability of two products (biosimilar and reference) of the relevant class should be demonstrated.

The non-clinical section of the product-class guidelines addresses the pharmacotoxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as the risk management plan. Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are also discussed.

The guidelines are by definition rather general, since no two cases are likely to be the same and the biosimilarity is assessed essentially on a case-by-case basis (see response to Question 1).

*Question 3.* Is an applicant able to submit an application for approval of a biosimilar for a reference product for which a product class guideline has not yet been issued?

Answer 3. Yes. The type and amount of pre-clinical and clinical data required will be determined on a case-by-case basis.

*Question 4.* Isn't it the case that applications for biosimilar products in Europe have been filed before the development and issuance of product class guidelines for those products?

Answer 4. Two products have been authorised so far under the EU framework on biosimilars<sup>1</sup>: The first is the growth hormone Omnitrope (somatropin), whose application was received by the EMA on July 1, 2004 and which was authorised by the European Commission in April 2006. The second is the growth hormone Valtropin (somatropin), whose application was received by the EMA on June 3, 2004 and which was also authorised in April 2006.

These two applications have indeed been filed before the product-class guideline on non-clinical and clinical issues for biosimilar products containing somatropin was developed (work on this guideline started in the beginning of 2005).

*Question 5.* Is an applicant able to consult with the EMA if a product class guideline has not been issued or if the applicant has an approach that differs from that in the guideline?

Answer 5. Yes, the applicant can indeed contact the EMA to discuss these matters.

*Question 6.* Isn't it the case that an applicant may deviate from a guideline so long as the applicant justifies the deviation?

Answer 6. In general, EU guidelines are not legally-binding, so an applicant may deviate from a guideline as long as he justifies the deviation. In the specific case of biosimilars, nevertheless, the EU legislation lays down that the type and quantity of supplementary data to be provided *must comply* with the related detailed guidelines. In other words, if the guideline is very prescriptive on one particular requirement, the applicant *must comply* with this requirement. However, existing EU

<sup>1</sup>The register of medicinal products for human use authorised by the European Commission is available at <http://ec.europa.eu/enterprise/pharmaceuticals/register/alfregister.htm>.

guidelines on biosimilars are usually general in nature and do not lay down highly prescriptive requirements, but rather recommendations (“the applicant should . . .”).

QUESTIONS OF SENATOR ENZI

*Question 1.* Thank you for your testimony and joining us today. As you know we are considering adopting similar legislation. As you have already implemented it, how long would you imagine it would take the FDA to implement similar legislation?

Answer 1. It is extremely difficult to predict how long it would take the FDA to implement similar legislation. This depends on a number of factors such as the type of products included within the scope of the regulation, the involvement of stakeholders, etc. I can only say that the scientific work necessary to put in place the current EU regulatory framework on biosimilars took the European Medicines Agency and the European Commission about 2–3 years.

*Question 2.* You mention in your testimony that the EMEA has rejected one application. Understanding that some of the information is confidential; could you describe why that was rejected?

Answer 2. One biosimilar application (Alpheon, an interferon) was indeed reviewed and given a negative scientific opinion by the EMEA in June 2006. One of the main reasons for this is that the EMEA had major concerns regarding the comparability of Alpheon and its reference product (Roferon-A), because of differences identified between the two medicines, such as impurities. The EMEA was hence of the opinion that Alpheon could not be considered as a biosimilar. The EMEA also had concerns that there was not enough data on the stability of the active substance and of the medicine that was going to be marketed. Also, the process used for making the finished medicine had not been adequately validated.

More scientific information on the evaluation of Alpheon is available on the EMEA website: [http://www.emea.europa.eu/pdfs/human/opinion/19089606\\_en.pdf](http://www.emea.europa.eu/pdfs/human/opinion/19089606_en.pdf).

*Question 3.* You indicated that your process of developing your law was an open process that included active participation of industry. Could you describe the benefit you saw in involving industry from the earliest point of developing the European legislation? Could you suggest any way to insure that legitimate scientific issues are considered but dilatory tactics do not derail the process?

Answer 3. Involving the industry, but also other interested parties such patients associations or healthcare professionals, enabled us to gather as much expertise in the field as possible (which, depending on the type of product concerned, may be limited). This allowed regulators and scientific experts at the EMEA/European Commission to confront their vision with the practical experience of manufacturers, doctors, etc. It also helped us to better understand which therapeutic areas and product classes are likely to emerge first in the field of biosimilars (e.g., insulins, growth hormones . . .).

Last but not least, involving both sides of the industry enabled a constructive exchange of contradictory views and facilitated the development of a balanced, unbiased regulatory framework. Transparent involvement of both the generics/biosimilar and the innovative industry, together with strong assurance of the independency of the scientific experts involved in the establishment and implementation of the regulatory framework, are in my opinion key factors to ensure that legitimate scientific issues are considered but dilatory tactics do not derail the process.

QUESTIONS OF SENATOR BINGAMAN

*Question 1.* To address the issues around substitution of one biologic for another, how would you recommend that data be obtained in the post market period to assure safety of both the innovator compound and the follow-on (or biosimilar)? Please discuss pros and cons of each potential stakeholder contributing to the data gathering process: manufacturer, third party payer, prescribing health professional, patient, regulatory agency.

Answer 1. Within the European Community, all products (innovative or biosimilar) made of recombinant DNA molecules—i.e., the vast majority of follow-on biologics today—are scientifically evaluated by the European Medicines Agency (EMA) and authorized by the European Commission. The EMA acts in close cooperation with the national authorities of the EU Member States and receives all relevant post-marketing information, e.g., suspected adverse reactions. The scientific analysis of the received information can affect the status of the product and lead to an amendment, suspension or revocation of the marketing authorization. It is

therefore a fully centralized system where the European regulatory Agency has a prominent role.

The holder of the marketing authorisation is legally responsible to ensure that all relevant post-marketing information is brought to the attention of the Agency. Patients are also encouraged to communicate any adverse reaction to health-care professionals. However, as the EU system for pharmacovigilance is currently under revision,<sup>2</sup> it is difficult to provide further details at this stage.

In my opinion, the issue of substitution is not specific to follow-on biologics, but is rather an issue for all biologics. It is expected that the likelihood of substitution, in practice, will be higher for biosimilars, but substitution can also happen (as it does currently in the EU) between innovative products. One key aspect to be considered when addressing post-marketing monitoring is traceability, which can easily be lost if suitable products' naming and prescription systems are not in place. In this regard, the data gathering process at the stage of the patient/health professional prescribing the product is particularly crucial to ensure not only that information is indeed gathered, but also that this information is accurate, usable and can be transformed into scientific knowledge on the concerned product.

*Question 2.* Can you propose a possible mechanism for communicating to stakeholders (above) during the process of post-market surveillance? Would different information go to different stakeholders at different times, or would all the information be equally accessible to all stakeholders?

*Answer 2.* The EU system is based on two levels: the first level concerns regulatory agencies, the second level affects the general public and healthcare professionals.

At the first level, it is essential that information is shared as fast as possible, with all regulatory agencies concerned. The European Medicines Agency acts as a focal point that gathers all post-market information and ensures information sharing and networking between Member States regulatory authorities.

At the second level, the information is usually released by the EMEA in a public manner, so it is equally accessible to all stakeholders. Typically, this second step is triggered only once the first level of information sharing between regulatory authorities has been completed and a way forward has been agreed. Information publicly released should be understandable for the whole public. In certain cases, it makes sense that two separate sets of information are released: one for specialists (healthcare professionals, prescribers), and one for the general public.

#### QUESTIONS OF SENATOR BURR

*Question 1.* Do you support the Clinton-Schumer bill in its entirety?

*Answer 1.* I am afraid that I am not in a position to answer this question. I can only underline the EU experience, which in my opinion demonstrates that the development of a regulatory framework and adapted scientific criteria to approve biosimilar products that are safe, of good quality and efficacious, is something feasible. As mentioned in my testimony, there is no reason in principle why the science should be different on the other side of the Atlantic.

*Question 2.* I am sorry to see that we do not have a witness testifying on the impact of the Clinton-Schumer bill on the financial viability of innovator biotech companies. If we did have such a witness, I think the witness would say that venture capital for biotech companies would dry up because this bill guts any drive for biotech companies to innovate. Why should a biotech company go through huge clinical trials, manufacturing challenges, studies, etc. to get a biologic approved when the day after approval a follow-on biologic company can send them a letter asking for a list of every single patent that is a part of making that biologic. And after providing that list, the innovator can only sit back and wait for the follow-on biologic company to submit an application at the FDA saying that their product is comparable to the innovator's product—not the same—but comparable. This bill has no data exclusivity for the innovator. There is no patent protection for the innovator. And there is no marketing exclusivity for the innovator. Why should venture capital firms invest in biotech companies if the companies have no guarantee of recouping their research investment? Mr. Rossignol, I would appreciate your comments on this concern.

*Answer 2.* The EU experience suggests that a regulatory framework that strikes the right balance between rewarding innovation, on the one hand, and allowing generic/biosimilar competition, on the other hand, is feasible and can effectively support the development of the biotechnology industry. It is also likely that the entry

<sup>2</sup><http://ec.europa.eu/enterprise/pharmaceuticals/index.html>.

of biosimilar products on the market will further stimulate innovators to develop new products or new versions of existing products.

The EU regulatory framework on biosimilars does not contain specific market exclusivity, data exclusivity or patent protection provisions for the innovator. Rather, it relies on existing, general provisions which apply in principle to all pharmaceuticals. I am not aware of any EU evidence demonstrating that the EU framework on biosimilars has deterred venture capital investment in the biotech sector.

It should also be stressed that one of the key goals—if not the most important—of any framework on biosimilars of follow-on biologics should be to protect patients' safety. In this regard, the EU innovative industry in Europe was rather supportive of putting in place a suitable framework on biosimilars, precisely to avoid double standards and make sure that biosimilars do not put patients' safety at risk.

RESPONSE TO QUESTIONS OF SENATORS KENNEDY, ENZI, AND BURR  
BY AJAZ S. HUSSAIN, PH.D.

QUESTIONS OF SENATOR KENNEDY

*Question 1.* Dr. Hussain, do you think it is possible for a manufacturer to present a data package that would justify FDA saying a follow-on product is interchangeable?

Answer 1. A complete data package on a follow-on product that demonstrates comparability at every level—structural, functional and clinical—with an innovator product, should be considered suitable for such a designation by the FDA. Such judgments are made every day by the Agency, when the sponsors of innovator products provide data to substantiate that their products are the “same” pre- and post-manufacturing changes, and the same regulatory standard can be applied by the Agency to follow-on products. In such instances with innovator products an achievement of comparability pre-supposes interchangeability. While in some cases the FDA will require analytical, preclinical and clinical data, this may not always be the case (especially as science and technology continue to improve), but in all instances it is a data-driven process in which the Agency already has extensive experience. Such comparability assessments have been used very successfully, with very few incidences of failure resulting in any loss of safety or efficacy in products reaching patients, and they have been critical to upgrading manufacturing capabilities for many existing biologics (both those regulated as drugs under FD&CA and those regulated as biologics under PHSa).

*Question 2.* Dr. Hussain, doesn't the FDA already make a finding of interchangeability every time it approves a manufacturing change? For instance, if a manufacturer were to change a cell line the FDA does not require that the manufacturer change the label or inform consumers that such a change has taken place.

Answer 2. If an innovator product uses a comparability protocol to make a manufacturing change, and the FDA is satisfied with the data provided on the pre-change and post-change material then the product is presumed interchangeable and there is no change in the label. The only indication that the batches are different will be the lot number so the material is fully traceable, but it will be invisible to the patient that any manufacturing change has occurred. And indeed, once comparability has been demonstrated, the patient can have confidence that the product will provide them with the same clinical outcome—that is the whole point of comparability and why it has been so successful for the manufacturers and the regulators for well over 10 years.

*Question 3.* Dr. Hussain, looking at the EU guidelines on different biosimilar products, we see that what the EU expects varies by product. For example, for insulin, the EU suggests only pharmacokinetic and pharmacodynamic studies to show efficacy. For growth hormone, the EU expects an adequately powered comparative effectiveness trial. Doesn't this variation show that, when we legislate, we need to give FDA the flexibility and discretion to ask for what it needs, and not write unnecessary requirements into law?

Answer 3. Just as FDA evaluates and approves innovator products, it is entirely appropriate that FDA be given the flexibility to require the data that they as experts believe to be necessary to fulfill the statutory criteria of safety and efficacy (for FD&C Act approved products) or safety, purity and potency (for PHS Act licensed products). The complexity of the products will determine the extent of the data required of a subsequent sponsor to establish comparability, and the European guidelines reflect this. However, we do not need to wait for FDA to promulgate guidelines, albeit they may choose to over time, as there is enough publicly available information with those biologics on which the patents are expiring for subsequent

sponsors to be able to propose follow-on candidates. It will be up to those sponsors to work with the Agency to assure them that their products are comparable. And indeed, as Mr. Rossignol, from the EU testified during the hearing, the science is global and so what has been learnt and discussed in Europe on the science, can also be employed here. Giving FDA the flexibility to adjust their requirements as the science evolves, but to leave the burden with the sponsors to assure that their products meet the appropriate regulatory criteria is entirely appropriate for follow-on biologics, just as it is for innovator biologics.

*Question 4.* Dr. Hussain, we all understand the importance of protecting innovation. Do you believe that allowing follow-on biologics is consistent with promoting innovation? Can allowing follow-on competition actually stimulate innovation in biologics?

*Answer 4.* I believe that there is nothing like competition to stimulate innovation, and nothing like perpetual monopolies to stultify it. Just as the Hatch-Waxman Drug Price Competition and Patent Term Restoration Act of 1984 led to an era of high productivity for both generic and innovator pharmaceutical companies, so I believe that the new regulatory pathway such as contained in S. 623 will stimulate innovation in both sectors too, not least because in addition to the competitive comparable/interchangeable pathways it explicitly contains a second generation pathway for innovators to facilitate their improvements to their own and each others already-licensed biologic products. A pathway based on established regulatory principals but that encourages the use of prior scientific knowledge by all sponsors is an ideal way to reduce inappropriate regulatory requirements and to stimulate innovation to the ultimate benefit of patients as well as the industries that serve them.

#### QUESTIONS OF SENATOR ENZI

*Question 1.* Thank you for your testimony. You note that you support the Clinton-Schumer bill as it will provide follow-on biologics to the market quickly. Would you support changes in the legislation that would address some of the concerns that you have heard today as long as they do not significantly delay competition in the pharmaceutical marketplace?

*Answer 1.* As long as the regulatory standards proposed in the legislation apply consistent and appropriately high regulatory standards to all biologics I would anticipate being supportive. However, I think the pathway proposed in the Clinton-Schumer bill is sufficiently specific to be reassuring to all sponsors that the FDA can apply its established regulatory experience, but flexible enough in its burden of proof remaining with the sponsor such that they are able to be creative and achieve the regulatory requirements with any data that they believe suitable—this basic conceptual approach will be hard to improve. Indeed it is the basis of the current PHS Act under which most biologics are currently licensed by the FDA, which has also proven remarkably accommodating to the massive progress in the technology.

Clearly, in addition to the pathway, it will always be important to respect legitimate intellectual property, but Novartis believes that patent issues can best be handled by the Courts, as is the case today for innovator PHS Act biologics, and should not be made a responsibility of the FDA who are neither qualified nor resourced to handle them. Thus, these patent issues should be “decoupled” from the pathway. Novartis would support some form of exclusivity for the sponsor of innovator products approved in the future, and used as the reference product for a follow-on biologic, whereby they would not face market competition for a set period post-approval. This could recognize the market uncertainties for these products, and as in the original Hatch-Waxman statute, enable the development of products with limited or no patent protection. Such an exclusivity would encourage the further creation of innovator products. However, data exclusivity is not a term we have used in our testimony because the follow-on product will not have access to, nor need, any of the data provided by the innovator to the FDA as part of their original approval.

What I would find questionable would be continued general debate that simply delays the recognition, which I am not sure anyone disputes, that ultimately the decision of the FDA must be on the individual application submitted to the Agency, and that this application by the follow-on sponsor will be confidential, just as that of an innovator sponsor. All that is needed is for FDA to have the requisite authority and the discretion to use it as warranted by the individual submissions they receive, irrespective of whether the sponsor is a traditional innovator company, generic company or some other equally competent sponsor. The quality of the application is what matters, and its evaluation by the FDA, not the general business model of the sponsor.

*Question 2.* Would you support other legislation that would bring follow-on biologics to the market quickly?

Answer 2. As long as the regulatory standards proposed in the legislation apply consistent and appropriately high regulatory standards to all biologics, and as long as intellectual property is appropriately respected, I would anticipate being supportive of a new pathway that enabled the FDA to approve interchangeable follow-on biologics. The timing, however, will be determined by when the sponsors of follow-on products submit their applications and the outcome of the subsequent review by the FDA. That is what will govern how quickly these products can be made available after FDA has been granted the necessary authority to review them.

*Question 3.* Novartis as a corporation operates in the European Union. You suggest that the data exclusivity of the European law should be inserted into the U.S. version of follow-on legislation. Could you discuss why you think expanded data exclusivity is preferable to patent extensions that are present in the Hatch-Waxman law?

Answer 3. The European Union has certain useful parallels in their Biosimilars Pathway (which was enacted into legislation in 2003), and through which Novartis obtained the first European approval of a biosimilars—Omnitrope, a recombinant Human Growth Hormone in April 2006. While, the market conditions in Europe are very different to those of the United States, and probably, as Mr. Rossignol indicated, have less relevance to the United States, than the pathway provisions, Novartis is a strong advocate for the protection of legitimate intellectual property worldwide. Part of intellectual property is patent protection, and part of this are the various forms of exclusivity, such as the European so called 8+2+1, whereby the regulatory authorities do not accept an application for 8 years, approve it for 10, and can grant a 1-year extension if a new indication is added. The system is not dissimilar to the Hatch-Waxman exclusivities of 4 and 5 years.

Biologics, licensed under the PHA Act are already entitled to and have received the patent-term extensions for which they became eligible under Hatch-Waxman. There are no distinctions in the patent term restoration provisions for drugs or biologics, or for FD&C Act products and PHS Act products. However, biologics cannot benefit from the exclusivity provisions on Hatch-Waxman as these do not apply to PHS Act products.

Further, I want to reiterate that I do not believe that any sponsor of a follow-on biologic will use the actual data of an innovator product, although they will need to refer to the already public prior finding of safety, purity and potency of the FDA, namely, the label of the innovator biologic product that they are referencing for comparability purposes. Thus, the rationale for data exclusivity is not protection against a subsequent sponsors' use of the data itself, but a term that refers to a preclusion on the FDA approving another product as interchangeable with a future innovator product for a certain period—and as such has been more accurately called market exclusivity. That is why I used the term market exclusivity throughout my testimony, and indeed it has value to the innovator as it is a greater assurance than patents which may be disputed and declared invalid or unenforceable in court (but prior to such litigation, their status cannot be guaranteed). Clearly the potential for patents extend for a longer period, and as such both patents and market exclusivities are valuable to the sponsors of biologic products, and as an incentive for further innovation.

*Question 4.* I understand that FDA recently approved Omnitrope as a “comparable” biotech drug, and that your application included clinical trials. In that application how many patients were enrolled? Could you describe the key differences in the approval in the United States and EU?

Answer 4. I am happy to address what is reflected in the public record. FDA-approved Omnitrope as a 505(b)(2) NDA under FD&C Act in May 2006. As such it was no different from other biologic drugs that have been approved by the Agency using this pathway, although we were the first case of a recombinant product that referenced a previously approved recombinant product. In our NDA we referred to the prior approval of an existing product and then we provided data, including clinical trials, to show that we were comparable (albeit this is not a term that is used in the Hatch-Waxman statute when 505(b)(2) was created). The same product, and the same set of data, that included analytical, preclinical and clinical data was approved in Europe under their Biosimilars pathway prior to the U.S. approval by FDA. The European pathway is based on comparability (CHMP/437/04: GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS. London, 30 October 2005).

To the extent reflected in the Summary Basis for Approval (SBA), and with the caveat that the studies continued for longer periods relative to the U.S. approval than would have otherwise been the case because of the delay in the approval, thus generating much more extensive data than the FDA or Sandoz anticipated.

*Question 5.* Currently the Clinton-Schumer bill has a few IP provisions that seem to tip the balance established in current law towards the generic companies. As Novartis is part generic part innovator, could you discuss the balance that is established in this bill?

*Answer 5.* As discussed above, in my answer to Question 3, we do believe that a balance of incentives for innovators will be important, as we create the new pathway that enables competing, interchangeable follow-on biologics. Indefinite monopolies for innovator products, even when all patents have expired, is not appropriate for biologics, any more than it was for drugs back in 1984 when Hatch-Waxman was enacted. Novartis believes in respect for intellectual property and competition, and believe that both will ultimately benefit patients through the greater availability of more and better medicines. Competition is the best way to ensure access to cost-effective drugs after patents expire, and we believe that the time has come for the authority to be granted to the FDA to approve Follow-on Biologics. These Follow-on Biologics will compete in the free-market, and newer and better ones will continue to be created, as long as it is to the same consistent, appropriately-high, science-based regulatory standards that apply to innovator products, and as long as legitimate intellectual property is respected. To the extent that market exclusivity can be provided to innovator biologics approved subsequent to enactment of any proposed legislation, we would anticipate being supportive, as we believe this gives a greater certainty to innovators, and as such will be a stimulus to their continued innovation.

#### QUESTIONS OF SENATOR BURR

*Question 1.* Do you support the Clinton-Schumer bill in its entirety?

*Answer 1.* Novartis does not support the bill in its entirety, however, as discussed in our testimony, we support the principles of the regulatory pathway proposed. Novartis supports the pathway proposed in the Clinton-Schumer bill because we believe that the FDA has proven their ability to use the comparability process for evaluating differences between biologic products in a manner that encouraged upgrading manufacturing and the increased availability of biologics without putting any patients at undue risk. We believe that they can be granted the authority to apply these same regulatory principles to the evaluation and approval of follow-on biologics, including interchangeable ones.

Novartis has not endorsed the intellectual property provisions in the bill. We do not believe that such provisions need to be in any way linked to the regulatory approval process—they can be as we say “decoupled” with the courts continuing to supervise patent disputes and FDA getting on with their job of reviewing and approving regulatory filings. Further, we think market exclusivity for the sponsors of future innovator biologic products should be included in the legislation.

*Question 2.* Under the Clinton-Schumer bill, the FDA has to lay out exactly what is wrong with a follow-on biologic application and tell the company what they have to do to fix the application. The FDA does not do that for any other company submitting an application for product approval (innovator biologic, generic, brand, animal drug, etc.). Do any of you support that language?

*Answer 2.* The regulatory criteria included in the Clinton-Schumer bill that form the basis for the rejection by the FDA of an application for a comparable product are derived from the Food, Drug, and Cosmetic Act Section 505 approval provisions for new drug approvals, albeit with tighter standards and more predictable operation and applying strict criteria and time lines. This will be to the benefit of all applicants for both comparable, interchangeable and second generation biologic products.

*Question 3.* Under current law, a company cannot choose the court they want to be sued in. In the Clinton-Schumer bill a follow-on biologic company can decide where they want to be sued. Do any of you support that language?

*Answer 3.* As a scientist and former regulator, I am not qualified by training or experience to address such a technical question of law and legal policy. Following receipt of the committee's questions, I have in these responses been consulting with my legal colleagues, and, upon receiving their input, could submit the views of the Novartis Group of Companies on this issue at a later date if that would be useful.



*Question 4.* The Clinton-Schumer bill permits the FDA to look at and use “any other information available to the Secretary” to determine whether a follow-on biologic is comparable to the innovator biologic. So the FDA could look at the innovator’s biologics licensing application for the data it needs to approve the follow-on. The fifth amendment to the U.S. Constitution protects trade secret data from use by the government without compensation. With the FDA’s current budget, do you think that the FDA has the funds to compensate the innovator company for using its data to approve another company’s application?

Answer 4. I am not a lawyer but it does not appear to me that anything in the Clinton-Schumer bill can or even aspires to override the trade secret restrictions that affect all applications to the FDA, innovator or generic, today. I think the reference to any other information to the secretary is any other public information, or any other information to which he already has access under the PHS Act, not any information that is protected and the property of another company, and simply in the possession of the FDA for the purposes of a regulatory review.

As discussed in my answers above, the innovators data is neither needed nor of interest to the subsequent sponsor of a Follow-on Biologic. At the point at which the legitimate IP has expired, the innovator product has been on the market for many years, if not decades, and it is certain that the technology available to produce the Follow-on Biologic will be vastly superior to that which was state-of-the-art at the time the innovator product was licensed. All the necessary data comparing the innovator product with that of the subsequent sponsor will have been developed by that subsequent sponsor in their own analyses and tests of commercially purchased innovator product compared head-to-head with their own candidate. The innovators own data would not be helpful as those tests would not have been conducted with the samples of the follow-on biologic, and the tests themselves, as well as the reagents will often also be proprietary to the original sponsor. As such the data to support the subsequent sponsors application will either be publicly available or the property of the subsequent sponsor. The FDA will not need any funds to compensate the innovator as they will not be using their data.

RESPONSE TO QUESTIONS OF SENATORS ENZI AND BURR BY SID BANWART

QUESTIONS OF SENATOR ENZI

*Question 1.* Thank you for your testimony. You note that you support the Clinton-Schumer bill as it will provide follow-on biologics to the market quickly. I assume that you would support changes in the legislation that would address some of the concerns that you have heard today as long as they do not significantly delay competition in the pharmaceutical marketplace?

Answer 1. Caterpillar supports legislation that would create an appropriate regulatory route for FDA review in a timely manner of biogenerics that are safe and effective. The Clinton-Schumer bill is the first measure in the 110th Congress to address this important issue.

*Question 2.* Would you support other legislation that would bring follow-on biologics to the market quickly?

Answer 2. Caterpillar welcomes the debate on this important issue and will review other legislative proposals as introduced.

*Question 3.* In your written testimony you have focused on the cost of the medicines without discussing the value of these medicines to your workforce. Do you measure employees satisfaction with the health plans? And how do you measure the value you are getting for your medical purchases?

Answer 3. Employees have an opportunity to provide feedback about our self-insured benefits plan on the value survey we conduct on a regular basis. Caterpillar does extensive benchmarking with comparator companies and our benefits packages consistently rank among the top quartile. We conduct rigorous analysis of the value of medical purchasing through the 6 Sigma process.

*Question 4.* Caterpillar is an innovative company and files for patents, presumably to prevent competitors from free riding on your Research and Development. I would assume you would be opposed to a law that would devalue your patents even if in doing so that would make mining equipment decrease in price. How would you distinguish that situation from this one?

Answer 4. Caterpillar supports a competitive marketplace and, upon expiration of its patent, Caterpillar expects and welcomes competition in the marketplace by others using the previously protected Caterpillar inventions. Such post-expiration use

of the patented invention is part of the bargain made by the patentee for the limited period of exclusivity provided by the patent laws.

In the area of patented biologicals, no competition exists using the patented invention after the patent expires because the FDA currently has no authority to approve biogeneric products in an abbreviated fashion. Caterpillar urges Congress to pass a bipartisan solution to create an appropriate regulatory pathway for FDA review of safe and effective biogenerics once a patent has expired or been held invalid.

QUESTIONS OF SENATOR BURR

*Question 1.* Do you support the Clinton-Schumer bill in its entirety?

Answer 1. Caterpillar supports legislation that would create an appropriate regulatory route for FDA review of biogenerics in a safe and timely manner. The Clinton-Schumer bill is the first measure in the 110th Congress to address this important issue.

*Question 2.* Under the Clinton-Schumer bill, the FDA has to lay out exactly what is wrong with a follow-on biologic application and tell the company what they have to do to fix the application. The FDA does not do that for any other company submitting an application for product approval (innovator biologic, generic, brand, animal drug, etc.). Do any of you support that language?

Answer 2. Caterpillar believes that the FDA should be given the authority to approve biogeneric drugs that are safe, effective, and provide additional value to the health of our employees.

*Question 3.* Under current law, a company cannot choose the court they want to be sued in. In the Clinton-Schumer bill a follow-on biologic company can decide where they want to be sued. Do any of you support that language?

Answer 3. Caterpillar does not have a formal position on this particular provision of the legislation.

*Question 4.* The Clinton-Schumer bill permits the FDA to look at and use “any other information available to the Secretary” to determine whether a follow-on biologic is comparable to the innovator biologic. So the FDA could look at the innovator’s biologics licensing application for the data it needs to approve the follow-on. The fifth amendment to the U.S. Constitution protects trade secret data from use by the Government without compensation. With the FDA’s current budget, do you think that the FDA has the funds to compensate the innovator company for using its data to approve another company’s application?

Answer 4. The Clinton-Schumer bill reflects language used in current law for new drug applications containing active ingredients (i.e., Hatch-Waxman and the Food, Drug, and Cosmetic Act) to create a parallel system for generic biologics.

Regarding the FDA’s budget, Caterpillar acknowledged in both its written and oral testimony the need for additional funding for the FDA to assume additional responsibilities associated with generic biologics. Excerpt from Caterpillar’s written testimony, page 6:

**4. Increase resources for the Food and Drug Administration.**

In order to adequately assume these new responsibilities, the FDA will need adequate resources. We support additional resources for FDA to secure more staff to ensure the timely review of biogeneric applications and the safety of biogenerics for consumers.

[Whereupon, at 11:50 a.m., the hearing was adjourned.]