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JOHNSON & JOHNSON

BEFORE THE SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

FOLLOW-ON BIOLOGICS

MARCH 8, 2007

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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 life-saving 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 non-follow-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 resulted in rapid clearance of the drug from the circulation. In yet other examples, a change as seemingly minor as placing a product in a prefilled 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 four years of extensive investigations involving more than 100 experts from clinical, pre-clinical, manufacturing, process sciences, logistics, quality, analytical, and regulatory fields and in excess of one hundred million dollars to identify the cause. The conclusion was 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 limitations 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 one patient in 1000, and a new drug had twice the risk, it would take a study of about 50,000 patients to have a good chance of detecting this important difference. 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 two 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 request 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 eight 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 ten-month deadline to complete review, potentially much longer to reach final action. Even priority drugs and biologics have a six-month review, and potentially take much longer to final action. The timeline of eight 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 workshops in which all parties were invited to offer input. The EU testing requirements do allow for abbreviations in testing where science and safety permit. 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.