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

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

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

I. Introduction

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

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

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

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

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

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

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

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

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

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

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

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

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

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

II. The Science Behind Patient Safety & Product Efficacy

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

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

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

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

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

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

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

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

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

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

a. Comparability – Manufacturing Changes

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

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

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

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

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

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

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

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

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

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

humans.

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

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

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

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

b. Immunogenicity

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

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

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

c. Interchangeability Critical to Addressing Costs

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

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

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

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

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

III. Recently Released FDA White Paper

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

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

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

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

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

IV. Summary

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

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

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

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

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

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

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