Testimony of

Mr. William Shultz

June 23, 2004

Chairman Hatch and Members of the Committee. Thank you for the opportunity to testify on the issue of access to affordable biopharmaceuticals. I am here today on behalf of the Generic Pharmaceutical Association ("GPhA"), the trade association whose 120 members produce more than 90% of all generic drugs sold in the United States.

Senator Hatch, for more than 20 years you have been a leader in Congress in efforts to ensure greater public access to affordable drug products. Your instrumental role in the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act") established the regulatory framework for generic versions of brand drugs regulated under the Federal Food, Drug, and Cosmetic Act ("FDCA").

It is fitting that you have taken the initiative to begin the discussion on how Americans can have access to generic versions of today's promising biotech medicines, which are manufactured by processes using biological organisms (or microorganisms). These drug products are referred to as "biopharmaceuticals."

As we all know, the Hatch-Waxman Act has been tremendously successful in providing Americans with access to affordable pharmaceuticals. As a result of this law, today there are more than 7,600 generic versions of the approximately 10,375 FDA-approved pharmaceuticals. And, more generic pharmaceuticals are approved every day. Let's take a closer look at the progress of affordable generics under Hatch/Waxman.

In 1984, generic drugs accounted for less than nineteen (19) percent of all prescriptions filled. Today, generic drugs represent more than fifty-one (51) percent of all prescriptions dispensed in the United States. In addition, even though generics account for more than half of prescriptions dispensed, generics account for less than eight cents of every dollar spent on prescription drugs. And of course the federal government, which purchases roughly 12% of all prescription drugs (costing nearly $21 billion in 2002) is the biggest consumer of all, and reaps enormous savings from generic drugs.

Passage of the Hatch-Waxman Act came at a critical juncture in America's efforts to make drug products affordable and accessible to consumers. In 1984, we were at a crossroads in terms of drug pricing and innovation in this country. At that time, we had a flourishing pharmaceutical industry that was developing innovative products, but was charging monopoly prices even after patents had expired. The Hatch-Waxman Act accordingly struck a balance between encouraging innovation and facilitating access to affordable medicines. And, by all measures, the 1984 Act has been successful on both fronts. The brand pharmaceutical industry has grown from a $19 billion industry in 1984, to a more than $200 billion industry in 2003. Simultaneously, the generic pharmaceutical industry has grown to where today over seven thousand FDA-approved

generic pharmaceuticals are on the market, saving this Nation's health care system tens of billions of dollars each year.

We are at a similar crossroads today with respect to generic biopharmaceuticals as we were in 1984 with respect to traditional pharmaceuticals. The generic pharmaceutical industry is convinced that the savings resulting from competition, and the incentive for brand companies to invest in innovation that also results in more new groundbreaking therapies, can be similarly applied to the biopharmaceutical industry.

As I turn to the important policy issues associated with access to affordable biopharmaceuticals, I would first like to note that, while the generic industry and FDA currently are engaged in discussions over the proper nomenclature for these products, for purposes of this hearing, we are referring to these products as "generic biopharmaceuticals."

Over the last 20 years, scientific advances have made the biotechnology industry an integral part of the pharmaceutical industry, producing essential, safe and effective biopharmaceutical products that meet critical medical needs for severely debilitating and life-threatening illnesses, such as multiple sclerosis, rheumatoid arthritis, and enzyme deficiencies. Historically, biological products have been products such as vaccines, blood, and anti-toxins regulated under the Public Health Service Act ("PHS Act"). Today, while many biopharmaceuticals are approved under the PHS Act, others are biotech products are approved under the Federal Food, Drug, and Cosmetic Act.

In 1984, the biopharmaceutical industry was still in its infancy, with only one biopharmaceutical product on the market. Today, more than 150 biotech drugs are on the market, including human insulin, interferons, human growth hormones and monoclonal antibodies. In the past year alone, more than 30 new biopharmaceutical drugs were approved. More than 600 products are in development and new products are being reviewed and approved by the FDA on a regular basis.

America's biopharmaceutical industry accordingly represents one of the most successful and fastest growing segments of U.S. healthcare. From 2002 to 2003, the pharmaceutical biotech industry enjoyed revenue growth in excess of 22%, compared to 11% for the total pharmaceutical market. In 2003, biotechnology products accounted for more than $33 billion in sales, or 12% of total pharmaceutical sales in contrast to the $ 8 billion sector of 1993. Moreover, analysts estimate that by 2010 biologic sales will exceed $60 billion.

Biologics are a major driver of increasing prescription drug costs. In 2003, six biotech pharmaceuticals -- Procrit, Epogen, Neupogen, Intron-A, Humulin and Rituxan --generated sales of more than $9.5 billion. The top three biotech pharmaceuticals: Neupogen, Epogen and Intron A cost at least $15,000, $10,000 and $22,000 per patient, per year, respectively. Moreover, Cerezyme, a biopharmaceutical drug product for an enzyme deficiency, costs over $170,000 per patient, per year. This drug was approved in 1994, and the product's cost will remain high in years to come without price competition. As evidenced by these examples, generic competition for biopharmaceuticals has the potential to offer consumers dramatic and substantial savings, while also lowering America's overall healthcare bill.

Currently, there are more than a dozen biopharmaceuticals for which U.S. patents have expired,

or will expire within the next two years. This number will only continue to increase as the pharmaceutical industry continues to develop more biotech products. The time is now to ensure competition for these very expensive biopharmaceutical products. Competition will not only result in consumers having access to more affordable prescription drug products, but also foster innovation in the biopharmaceutical industry: a win - win situation for all.

In short, Mr. Chairman, today we are at a crossroads similar to the crossroads Congress faced in 1984. In 1984, as now, there were a significant number of brand drugs on the market for which patents had expired but for which there was no generic competition. Today is roughly 20 years since the first biopharmaceuticals were approved. As was true for post-1962 chemical drugs in 1984, even where patents have expired, FDA requirements are a regulatory barrier to competition and lower drug prices. And just as in 1984, the biotechnology industry adamantly opposes competition, even after their patents have expired.

In 1984, FDA and Congress recognized that a new regulatory system for generic drugs made sense. Today, it is widely recognized that a program providing for the approval of generic biopharmaceuticals makes sense as well. As former FDA Commissioner Mark McClellan recognized this year, "we do believe that the science may be adequate now to proceed on several relatively simple biologics that were approved as NDAs, and hence are subject to Hatch-Waxman laws." The same science recognized by Dr. McClellan also applies to products approved under the Public Health Service Act.

Even as we are debating how to codify a regulatory paradigm for generic biopharmaceuticals, other countries are actively implementing such programs, including countries in the EU, Asia and Latin America. In fact, the EU issued guidance three years ago to assist the industry in bringing generic biopharmaceuticals to the market. At least one company in our membership has been distributing generic biopharmaceuticals for over a decade in at least 15 countries around the world. These products have demonstrated safety and efficacy. As the world leader in pharmaceutical development, the U.S. should be willing to take on a leadership role in the development of a viable framework for generic biopharmaceuticals. If Congress does not act now, Americans will continue to be faced with escalating drug prices, while others reap the benefits of affordable biopharmaceutical products.

The brand companies have argued that it is not even worth debating the legal contours of a regulatory system for generic biopharmaceuticals because, as a matter of science, no such system is possible. We disagree. First, as FDA has recognized, there is already a scientific basis for some generic biopharmaceuticals. In addition, as the brand companies are well aware, when a company is given an incentive to develop new technologies or scientific approaches to seemingly intractable problems, innovation that surmounts these obstacles will usually follow. Thus, it is crucial that a regulatory system for generic biopharmaceuticals be codified that creates incentives for generic companies to engage in the research and development of generic biopharmaceuticals. With these incentives in place, we are confident that many of the allegedly insurmountable scientific obstacles to generic biopharmaceuticals will soon fall by the wayside.

We recognize that FDA is not likely to act without direction from Congress in the form of legislation. GPhA believes FDA currently has the legal authority to approve generic

biopharmaceuticals with less than the full set of pre-clinical and clinical data required for the approval of the brand product. This is not the place to set out an elaborate legal analysis, but there are a number of bases for such authority. First, certain biopharmaceuticals, such as Insulin and Human Growth Hormone, are already regulated under the FDCA and are subject to the Hatch-Waxman Amendments. To the extent that generic biopharmaceuticals may not qualify for approval under the basic generic approval provision in the statute (section 505(j) of the FDCA) because simple blood level studies are not sufficient to establish equivalence, they would qualify under a separate provision of the Act, known as "section 505(b)(2)."

Under section 505(b)(2), FDA can rely on its earlier approval decision of the brand product, and then require additional data, as appropriate, to confirm that the generic product is safe and effective. FDA recently upheld the use of section 505(b)(2) in this regard. The brand-name pharmaceutical industry disagrees with this interpretation of section 505(b)(2). In response, I would point out that this has been FDA's consistent interpretation of the law since it began issuing regulations to implement the Hatch-Waxman Act.

It is true that today the FDA regulates most biopharmaceuticals under the Public Health Service Act, which, as previously discussed, is not part of the Hatch-Waxman regime. But the Public Health Service Act has for many years contained a provision stating that nothing in that Act shall affect the FDA's jurisdiction under the FDCA, and it is clear that FDA could regulate all biopharmaceuticals under the FDCA, as it had chosen to do for insulin and human growth hormone. In fact, Congress made this point explicit in 1997 when, in the Food and Drug Administration Modernization Act, it changed the PHS Act to state directly that the FDCA applies to biological products subject to regulation under the PHS Act.

Precedent exists for the approval of biopharmaceuticals with reduced pre-clinical and clinical data packages under the PHS Act. These biotech products include Hepatitis B vaccines and the Hemophilus influenza type B vaccine, among others. It is our understanding that allergenic extracts, crude biological products derived from plants and animals also have been approved under this legal mechanism with limited pre-clinical and clinical data. In addition, FDA allows for interchangeability for products approved under this Act. For example, the FDA-approved labeling for GlaxoSmithKline's yeast-derived Hepatitis B vaccine states that this product is comparable and interchangeable to other Hepatitis B vaccines derived from yeast and blood plasma. This interchangeability allows the health care practitioner to select among a wide variety of Hepatitis B vaccines produced from various cell sources and manufacturing processes to complete a course of immunization in healthy patients, including children. Thus, FDA has approved biopharmaceutical products under the PHS Act which are supported by abridged pre-clinical and clinical data sets, and, in at least one instance, has deemed the product interchangeable with other comparable brand products.

A principal argument advanced by the brand-name companies in opposition to a system for the approval of generic biopharmaceuticals is that such a system would be unconstitutional because it would amount to a taking of their property without just compensation. In fact, one brand-name company, Genentech, recently filed a citizen petition with the FDA in which it made the extraordinary argument that the FDA could not even issue guidance on data requirements for the marketing of generic biopharmaceuticals. As I understand it, Genentech's argument is that FDA

has gained certain expertise after reviewing submissions by Genentech and others and that, regardless of whether it releases the actual information supplied by the brand companies, it may not even use the experience and knowledge it has previously gained in the review process to draft a guidance document on data requirements for generic biopharmaceuticals. Of course, this argument is counter to FDA's long-standing position on guidance documents. That is, an FDA guidance "represents FDA's current thinking" on a specific topic. This "current thinking" represents the Agency's cumulative knowledge to advance science. Even if FDA were to release the information after the brand company's patents had expired, release of such information would not constitute an unconstitutional taking under controlling Supreme Court case law. GPhA is having a thorough constitutional analysis prepared on the taking issue and will submit it to interested members once it is prepared.

Nevertheless, I want to emphasize that in case of the use of section 505(b)(2) of the FDCA, the FDA is simply proposing to reduce the data requirements for generic biopharmaceuticals based on its approval of the brand product. It would be relying on the knowledge gained of the brand product, but not on the actual data submitted by the brand company. Thus, on its face, there is no basis whatsoever for the takings argument advanced by the brand-name companies.

The implications of the brand industry's argument that the Constitution prohibits FDA from relying on its own decision to approve a brand product, and that Congress could not enact legislation directing or authorizing FDA to do so, are wide-ranging indeed. If accepted, these arguments would raise constitutional doubts about the status of a significant number of FDA and other regulatory agency programs. In certain regulatory programs, such as those covering food additives, medical devices, and over-the-counter drugs, FDA allows the entire industry to rely on an FDA approval based on test data submitted by regulated companies. Of course, companies are always subject to the limitations of patent laws.

Another argument put forth by the brand industry is that the science is unavailable to detect changes in protein structure between the brand product and the generic biopharmaceutical product. Yet, this contention ignores the fact that analytical scientific techniques and methods have rapidly advanced over the past decade. Comparative studies between the brand biopharmaceutical product and the generic biopharmaceutical have shown similarity in the primary, secondary, and tertiary structure of these products. It is possible today to demonstrate that the identity of these molecules correspond to the brand product. Biological activity has been shown to be consistent with international standards, including NIBSC (National Institute of Biological Standards) and WHO (World Health Organization), and published data from the brand products. Impurity profiles, both process and product-related, can be determined for generic biopharmaceuticals as well as for brand pharmaceuticals.

Generic biopharmaceuticals also are manufactured in the same manner as brand biopharmaceuticals. Changes to the manufacturing process for generic biopharmaceuticals are addressed in the same manner as brand manufacturers in that comparability between the product prior and subsequent to such change is established. In short, generic firms approach safety, purity, potency, quality and manufacturing using the same scientific principles and standards as those relied upon by the brand sector.

Immunogenicity is another concern mentioned by brand manufacturers. We acknowledge that protein products are inherently immunogenic to some extent. FDA has put forth a risk-based approach for evaluation of immunogenicity. Although this approach was not created for a risk assessment of generic biopharmaceutical products, the elements of the approach can be extrapolated for this purpose. These elements include the knowledge that a manufacturer has of its product; the structural difference between the generic biopharmaceutical and the brand product and the ability of current technology to detect this structural change, if any; clinical relevance of bioassays (a measure of effectiveness), process and product impurity profiles, and the immunogenic potential of the protein. Such an approach would allow FDA to establish approval criteria regarding product safety on a product-by-product risk assessment basis.

Testing requirements also should vary depending on the complexity of the product. For example, a simple protein, such as interferon, should have a reduced pre-clinical and clinical program when compared to a glycosylated protein (proteins with sugar molecules), such as erythropoetin. Much data exist on the interferons: their protein structure, binding sites, and mechanism of action are well-known; the manufacturing process is understood and consistent; and, as these are redundant endogenous proteins, the immunogenicity profile is one in which adverse events are to be expected, but when they do occur, they are usually not life-threatening. Erythropoetin, on the other hand, is more complex due to glycosylation sites; and the immunogenicity profile for this unique endogenous protein is one where adverse events are rare, but serious. Accordingly, generic biopharmaceuticals should have a reduced pre-clinical and clinical program based on many factors, including those mentioned above. In fact, this approach has been publicly put forth by FDA as recently as 2003 for Human Growth Hormone and Insulin.

The Committee will want to carefully consider the appropriate design of a regulatory system that allows for generic biopharmaceuticals. In this regard, I would make several points.

First, the system needs to allow FDA the flexibility to tailor pre-clinical and clinical data requirements for biopharmaceutical products. The complexity of these products vary along a continuum, and FDA should have the authority to establish its requirements based on a scientific risk-benefit approach.

Second, Congress needs to direct FDA to impose only the regulatory requirements that are necessary to ensure similarity to the brand product and thus ensure that the affordable biopharmaceutical is safe and effective for its intended use. In 1984, Congress was concerned that FDA would impose burdensome requirements, and it included provisions in the Hatch-Waxman Act to address this concern. We urge Congress in drafting generic biopharmaceutical legislation to be mindful of the same concerns. And, Congress and FDA also should be mindful that ethical principles require that pre-clinical and clinical testing be required only where such tests are necessary to demonstrate safety and effectiveness.

Third, we urge Congress to direct FDA to play an active role in advising the generic biopharmaceutical companies about study design, data requirements and other issues, as it currently advises brand companies seeking authorization to market their products. Generic biopharmaceuticals will benefit consumers and healthcare providers and they will result in significant savings to federal government. It is in the public interest for FDA to offer constructive

advice to companies seeking to develop these products, and to provide such advice early in the process and in a timely manner.

Finally, once Congress enacts legislation, we would urge it to monitor FDA's progress in implementing a generic biopharmaceutical program. Periodic reports to Congress may be appropriate. Unlike the approach that Congress imposed for chemical drugs, here it will be necessary that any legislation provide FDA with the flexibility to calibrate the regulatory requirements to the complexity of particular products. Unfortunately, this creates a risk of unnecessary regulatory burdens and, for that reason, periodic Congressional oversight may be necessary.

In conclusion, Chairman Hatch and members of this Committee, we ask for your help. As a result of the 1984 Act, the generic drug industry now includes highly sophisticated and well-capitalized companies that are ready to enter this market. Scientific knowledge and technology have advanced to the stage where there are major biopharmaceutical products for which generics exist around the world. Yet, the lack of a clear and efficient regulatory pathway here at home hinders not only imminent product approvals, but also product research and development.

Last fall and earlier this year, FDA was proceeding to issue a draft guidance, which would have begun the discussion about the appropriate regulatory requirements for generic biopharmaceuticals. Unfortunately, earlier this month, the agency announced that that guidance will be delayed until at least next fall. Meanwhile Genentech has suggested in its citizen petition that it will sue FDA even if the agency issues only a draft guidance.

In other words, Mr. Chairman, we are at a standstill. The case for generic biopharmaceuticals is every bit as strong as was the case for generic drugs in 1984. As we stated above, the use of biopharmaceuticals is expected to increase dramatically over the next decade. The introduction of generic versions of these important products would translate into a significant cost savings for the consumers who need them. Once the patents on these products have expired, it is essential that there be a clear regulatory pathway and that FDA regulatory requirements not be a barrier to competition.

This problem demands your attention. The generic industry stands ready to assist in any way we can, and we thank you for holding this hearing. I would be happy to answer any questions.