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Committee on Oversight and Government Reform  
Safe and Affordable Biotech Drugs — The Need for a Generic Pathway

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Good morning Chairman Waxman, Ranking Member Davis and Members of the Committee. My name is Theresa Gerrard. Thank you for allowing me the opportunity to testify this morning on the importance of establishing a science-based abbreviated approval pathway for biogenerics. As a scientist and a former FDA official, I believe that an abbreviated approval pathway can bring to patients affordable biogenerics that are, above all, safe and effective.

By way of introduction, I graduated from Cornell University where I majored in Biochemistry and I received my Ph.D. in Immunology from Virginia Commonwealth University's Medical College of Virginia. My postdoctoral training was at the National Institute of Allergy and Infectious Diseases, NIH where I trained under Dr. Tony Fauci. My research was focused on understanding human immune response to antigens. From 1984 to 1995, I was with the FDA in various positions from Staff Fellow to Division Director for the Division of Cytokine Biology. This Division is now called the Division of Protein Therapeutics. I was the Chairman of the licensing committee for Amgen's Neupogen, Genentech's Interferon-gamma and oversaw the licensing of Chiron's Betaseron and Biogen's Avonex. As the Division Director, I was responsible for the regulatory and research activities of the Division, which included review of INDs, BLAs and postmarketing actions for cytokine products such as interferons and growth factors. While at the FDA, I was involved in developing policies on the comparability of well-characterized products. It is fair to say that I reviewed hundreds of biotech products during my tenure at the Agency.

After leaving FDA, I was Director of Development for Amgen in Boulder, CO where I had oversight of clinical and product development for several recombinant protein products. We developed clinical programs, regulatory strategies and resolved product and manufacturing issues for biotechnology products for rheumatoid arthritis, hepatitis C, and oncology. I also served as the clinical team leader for consensus interferon (Infergen). This included filing an FDA license application, analyses of ongoing studies, and planning for postmarketing studies.

Since 1998, I have been an independent consultant to biotechnology and pharmaceutical companies. I have worked with many companies, primarily brand or innovator companies, in the areas of regulatory strategy and product development. I have worked with many companies in reviewing manufacturing changes during development and after FDA approval and have evaluated the manufacturing changes as part of the overall clinical development program. I have worked on many chemistry and manufacturing issues for protein therapeutic products and have also been involved in the

clinical development for many products. During the past 10 years, I have authored a number of papers and presented lectures on manufacturing changes, comparability and immunogenicity.

My testimony today will focus first on the role of analytical testing in the characterization of biopharmaceuticals and the determination of comparability to ensure safety and efficacy. I will also address the issue of immunogenicity.

### ***THE SCIENTIFIC ADVANCEMENT OF ANALYTICAL TESTING***

Every biological product is subjected to rigorous analytical testing. The same would hold true for biogenerics. Analytical testing consists of multiple tests that are used to assess the physical, chemical and biological characteristics of the product. Many more tests are used to assess a biologic than are typically used to assess a drug. This battery of tests is conducted for every batch of biopharmaceutical product manufactured and is also used to monitor the product during the manufacturing process. In the field of biopharmaceuticals both the Food and Drug Administration (FDA) and industry rely on analytical testing to ensure consistency so that every batch of the biopharmaceutical will be deemed safe and effective for its intended use.

Many biologics, including almost all of the biotech products, can be now defined by chemical and physical attributes. This fact can be attributed to two scientific advances. The first is the increasing purity of biological products, especially recombinant biotech products. The production of human proteins through recombinant technology continuously improves, providing ever more highly purified human proteins. The second advance is the increasing sophistication of the analytical technology that allows a very detailed characterization of these products. Although the cells that are used to produce biopharmaceuticals are complex living organisms, all finished biopharmaceutical products used to treat patients are highly purified human proteins that are produced consistently using advanced manufacturing technologies. The large array of sophisticated analytical tools that exist today now allow for the characterization of biopharmaceuticals to ensure safety and efficacy.

The advances in analytical characterization and the ability to assess the specified or well-characterized biologicals by analytical tests allowed FDA to develop scientific policies on comparability in the early 1990s. These policies gave brand manufacturers the ability to change the manufacturing process without the need for clinical trials if the new product was shown to be comparable to the previous product. Prior to this time, every change in a manufacturing process necessitated the need for new clinical data. It was the innovator biotech manufacturers who pressed FDA for this change, because they rightly claimed that their biopharmaceuticals were so well characterized. They proved this through their ability to identify potential product changes with analytical testing technology.

The brand companies fought for these policies because the need to make manufacturing changes for biotech products was common and manufacturers wanted to

make changes to the manufacturing process without the need to repeat clinical trials. FDA agreed that the nature of the products allowed manufacturing changes to be assessed predominantly by analytical testing for characterization. In fact, and this is a critically important point, FDA recognized that analytical testing was far more sensitive in the ability to detect product changes than a typical clinical trial. For the past 15 years, manufacturers of well-characterized biopharmaceuticals have been able to make manufacturing changes without repeating clinical trials if they demonstrate that the product made after the manufacturing change is comparable to the product made before the change.

Prior to 1996, FDA placed as much emphasis on licensing the manufacturing site as it did on characterizing the final product. In particular, CBER required both a Product License Agreement (PLA) and an Establishment License Agreement (ELA) for product approval. The ELA was specific to the facility and process used for that product. When FDA stopped requiring ELAs, it acknowledged a significant shift in the agency's understanding regarding the assessment of biopharmaceuticals. This change in policy signaled FDA's growing confidence in its ability to determine comparability, and thus, safety and efficacy, based on results from analytical testing of the finished product, independent of the manufacturing process. FDA also recognized that changes to the manufacturing process were common in the industry and that in most cases analytical testing could support these changes without need for retesting the product in clinical trials.

### ***COMPARABILITY***

When we speak of biologics, the focus is on comparability—no two batches of a biologic product, whether brand or generic, will be identical. Therefore biologics should always be discussed in the context of comparability. What does demonstration that two products are comparable mean? Successful demonstration of comparability between two biopharmaceuticals produced by different manufacturing processes does not necessarily mean the two products are identical in every way. Minor differences in the products manufactured by two different processes will be noted, however the products will be comparable. Likewise, biopharmaceutical products often undergo changes after approval and the pre-change and post-change products will be comparable, not identical. The fact is that every batch of a brand biopharmaceutical is simply not identical to the previous batch, but FDA establishes boundaries and all batches must fall within the established boundaries for that product.

Answering the question, “what is comparable” is determined on a case-by-case basis using multiple analytical tests to characterize the physical and chemical attributes of biopharmaceuticals. These analytical tools allow manufacturers to determine essential characteristics such as the sequence of amino acids, secondary and tertiary structures, and purity, among other physical and chemical features. For simple proteins, such as interferons, defining and demonstrating comparability is fairly simple. Alpha interferons are small proteins without glycosylation so analytical testing of the amino acid sequence, purity, bioactivity and aggregation is relatively straightforward. On the other hand,

complex proteins, such as antibodies, would need additional testing (e.g., carbohydrate analyses and glycoform heterogeneity) because these are larger and are glycosylated (have sugar molecules on the protein).

It bears mention that analytical testing is only one method for establishing the comparability of biological molecules. The amount of data needed to demonstrate comparability may depend on the complexity of the product and the significance of the manufacturing change. Analytical testing is regarded as the most precise measure of a molecule's attributes and thus serves as the first tier for comparability determination. If product differences are observed in analytical testing, then additional preclinical or pharmacokinetic tests may be warranted. Other methods include human pharmacokinetic and pharmacodynamic testing, and even clinical trials. This is dealt with on a case-by-case basis within the FDA. Often a tiered approach is used to assess products. If differences are observed after additional testing, or if there is insufficient product knowledge of the impact of differences, FDA has the discretion to ask for data from clinical studies or decide that products are not comparable and, therefore, not approvable.

As stated earlier, it is common for brand biopharmaceutical companies to implement manufacturing changes. It would be impracticable or impossible to make manufacturing changes if it resulted in undetectable changes that affect the product's safety or efficacy. In other words, if the complexity of biopharmaceuticals were as daunting as some maintain, then the current explosion of new biopharmaceuticals would be impossible. Manufacturers faced with unknowable or insurmountable complexities would simply not be able to assure consistency in the production of multiple lots of their biopharmaceutical or to assure comparability after changes to the manufacturing process.

During the past 15 years, FDA scientists have gained substantial experience and expertise in assessing manufacturing changes and comparability data for a large number of proteins. These range in complexity from the simple, low molecular weight, non-glycosylated proteins, such as insulin to complex, high molecular weight, glycosylated proteins, including monoclonal antibodies. The FDA allows the use of analytical testing to establish product comparability even following major manufacturing changes. For instance, in the case of Biogen's Avonex and InsMed's Iplex, the manufacturers changed the cell line, and the purification scheme and additionally for Avonex, the manufacturing site. In both cases, pre- and post-change product comparability was demonstrated to FDA's satisfaction without need for clinical trials to approve the post-change product.

Both Avonex and Iplex are complex products. The well-established methods for making comparability assessments allow biopharmaceutical manufacturers to change manufacturing sites, host cells, purification processes, and other aspects of production while ensuring that the products remain comparable from year-to-year and batch-to-batch. In another example, data presented on several manufacturing changes for Enbrel, a complex glycoprotein used to treat arthritis, noted that such changes were implemented after demonstration of comparability that included analytical and pharmacokinetic data.

FDA's policy on comparability has been very successful in ensuring safety and efficacy and has allowed brand manufacturers to implement manufacturing changes to bring products to market sooner. The underlying scientific principles that guided comparability policy are still valid and could be adopted for generic biopharmaceuticals. The primary premise is that analytical testing is the most sensitive method to detect differences between two products. Clinical trials are rather insensitive in detecting product differences because the variation among people in their response to a biopharmaceutical does not allow one to detect subtle product differences. However, FDA has the discretion to require any data that is needed to assure the safety and efficacy of the generic biopharmaceutical including clinical trials.

Undoubtedly, comparability will involve studies of the primary structure of the protein (that the requisite amino acids are present in the proper sequence), studies of potential changes to those amino acids (such as oxidation or deamidation), and that the protein has the proper three-dimensional structure ("folded" correctly). Comparability will also involve studies to show that the innovator and biogeneric proteins have a comparable level of purity. Comparability may also include testing to show that the innovator and biogeneric proteins have similar behaviors in biological assays. Again, FDA has established rigorous standards to assure that all biopharmaceuticals, irrespective of manufacturing processes, are safe and provide expected efficacy benefits to patients.

While state-of-the-art analytical technologies are the cornerstone for establishing comparability, such determinations may also be based on a variety of other testing methods. As I mentioned, pharmacokinetic, pharmacodynamic and/or confirmatory abbreviated clinical studies are currently used to address the specific concerns related to certain products.

The available spectrum of comparative tests would allow comprehensive evaluation of brand and biogenerics. With FDA's extensive experience in evaluating comparability data, it is possible to extend the concept of demonstrating comparability through non-clinical studies to the approval of biogeneric. Just as it currently does when brand companies make changes and comparability cannot be determined, FDA could require more data, including clinical studies, or not approve a biogeneric if it determined that comparability was not established through analytical testing to determine safety.

### ***IMMUNOGENICITY***

The question of immunogenicity has been raised in the discussion of both brand biopharmaceuticals and biogenerics. Therefore, I thought it was important to provide a scientific assessment of immunogenicity. Immunogenicity is the ability of a substance to stimulate the body's immune response, which usually means the generation of antibodies that are specific to the substance. The generation of antibodies to foreign substances, such as bacteria, is a normal response in keeping people healthy. People routinely make antibodies to many different substances and experience no negative effects. Sometimes a biopharmaceutical can cause people to generate antibodies, which are specific to that

biopharmaceutical. This sometimes occurs even though the biopharmaceutical is a highly purified human protein and is the same as the natural human protein.

In most cases, the antibodies to biopharmaceuticals are only temporary and have no adverse consequence. Even with antibody formation, most patients can continue to be treated effectively with the biopharmaceutical and there will be no difference in the side effects. The development of immunogenicity is never a reason to discontinue treatment with a biopharmaceutical unless there is reason to believe that the antibodies have rendered the biopharmaceutical or its natural counterpart ineffective. This situation is very rare.

Most impurities found in biopharmaceuticals today exist in minute amounts and do not cause immunogenicity. One factor that commonly has been associated with the immunogenicity of biopharmaceuticals is aggregation. Aggregation occurs when proteins interact to form large clusters of molecules. Aggregation can and should be monitored in the analytical testing of every lot of biopharmaceuticals and as part of the stability program over the shelf-life of the product. Many brand biopharmaceutical products were approved in an era when the importance of testing for aggregates was not recognized and, therefore, there is often no assessment of aggregates. Frequently, the analytical test procedures for the brand biopharmaceutical have not changed in many years and sometimes have not changed since the original FDA approval. Today, there are several methods available to test for the presence and size of aggregates. Biopharmaceuticals that would be approved by the FDA today, including biologics, would include this important testing for aggregation as a way to minimize any potential risk of immunogenicity.

There is no reason to believe that a biologic would have greater immunogenicity than the brand biopharmaceutical. Even if a generic manufacturer uses a different method to produce the biopharmaceutical, every lot of the biologic would be carefully analyzed and tested to assure that the product is safe and that any impurities such as aggregates, that might be associated with immunogenicity, are removed. FDA carefully reviews the manufacturing process for generic drugs; how these drugs are tested; and the results of the analytical tests. FDA would do the same for biologics as well. As stated earlier in my testimony, FDA has significant experience in the review of many types of biopharmaceutical products and the analytical methods to characterize these products. Moreover, with a biologic, the FDA has the benefit of many years of marketing history and a record of the safety and immunogenicity of the brand biopharmaceutical. Since the biologic would be analytically comparable to the brand product then immunogenicity would be expected to be similar.

FDA has more than two decades of experience with evaluating brand biopharmaceuticals for immunogenicity. Therefore, FDA can assess the risk when it reviews the products for purity, safety and overall quality. When the need arises, FDA can request additional testing including clinical testing to assess immunogenicity. While immunogenicity is an important consideration for biologics, it is certainly not a hurdle to their development. For those limited situations when additional supporting data is

required, clinical testing can augment comparability and aggregation studies. Finally, generic biopharmaceuticals will be subject to the same post-approval surveillance requirements as brand products that monitors patient safety.

### ***SUMMARY***

The science exists for the creation of a clear, efficient abbreviated approval pathway for biogenerics to ensure safety and efficacy. FDA currently reviews the data from sophisticated and advanced scientific analytical tools to assess the impact of changes made by the brand industry to their biopharmaceutical products. These analytical tests have been deemed to be the most sensitive technologies to ensure safety and efficacy of products that are changed by the brands. Moreover, this well-established approach to testing, used routinely by the brand industry, has significantly reduced the need for clinical studies and has resulted in bringing safe and effective life saving biopharmaceuticals to consumers.

Using the same scientific principles that were the basis for this current effective process for testing comparability, it is scientifically sound and practical to approve biogenerics based on a clear and efficient abbreviated approval pathway that will ensure safety and efficacy.