WRITTEN STATEMENT OF

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Hearing on Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States

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Good morning, Mr. Chairman and Members of the Committee. My name is Dr. David Schenkein and I am vice president of Clinical Hematology and Oncology at Genentech, a leading biotech company headquartered in South San Francisco, California. I am pleased to come before you today on behalf of the Biotechnology Industry Organization (BIO) to offer my perspective on the issues relevant to any proposed framework for the abbreviated approval of follow-on biologics.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of health care, agricultural, industrial and environmental biotechnology products.

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 while preserving patient safety and incentives for biomedical innovation.

By way of introduction, I have been a medical oncologist and hematologist for over 20 years. I have spent most of my career caring for patients with life threatening illnesses. It's been my job to sit with patients and their families and make decisions on the most appropriate therapy to choose --- many times a choice of risk benefit that has life and death implications. Prior to joining Genentech, I spent 17 years in academic and clinical medicine as an attending physician in Hematology Oncology at the Tufts-New England Medical Center in Boston, where I was an associate professor and held the position of director of the Cancer Center. I will soon be on the oncology faculty at the Stanford Cancer Center.

I previously served as the senior vice president of Clinical Research at Millennium Pharmaceuticals in Cambridge, where I oversaw the clinical development of Velcade, a first-in class cancer therapy now approved to treat multiple myeloma and non-Hodgkins lymphoma. In my current role at Genentech, I am responsible for leading the medical and scientific strategies for our BioOncology portfolio, including overseeing the development of a robust pipeline of novel cancer therapies and marketed products, including Avastin, Herceptin, Rituxan and Tarceva.

My company, Genentech, is considered the founder of the biotechnology industry. Genentech was founded 31 years ago with the goal of developing a new generation of therapeutics created

from genetically engineered copies of naturally occurring molecules important in human health and disease. Within a few short years, Genentech scientists proved it was possible to make medicines by splicing genes into fast-growing bacteria that produced therapeutic proteins.

Today, Genentech continues to use genetic engineering techniques and advanced technologies to develop medicines that address significant unmet needs. Genentech is among the world's leading biotechnology companies, with 14 products on the market for serious or life-threatening medical conditions, over 50 projects in the pipeline and more than 10,000 employees.

The researchers and clinicians at Genentech are working to fundamentally change the way cancer is treated by developing a broad portfolio of innovative targeted therapies designed to improve and extend the lives of cancer patients. Put simply, we are trying to end the death sentence that cancer currently represents by creating medicines that will transform cancer into either a curable illness or a chronic condition. We strive for the time when a diagnosis of cancer leads to a discussion similar to the one that occurs today around high blood pressure or diabetes.

I would like to begin by noting that I appreciate the concern Congress has shown for patient access to biologic therapies. It is a concern that I share — as does Genentech, and as does BIO. While legislation on follow-on biologics has the potential to increase access to some medicines, that legislation must be well-founded in science and ensure that the medicines to which access is provided are no less effective or safe than medicines already on the market. I believe that through the proper process, those critical goals can be met.

In order to ensure that new pioneer biotechnology products continue to reach patients and physicians, it is essential that Congress adopt six key principles as it explores the creation of any

regulatory pathway for follow-on biologics. I will touch on these principles in my testimony, but will focus principally on the first three since my expertise is as a physician and a scientist.

- **Ensure Patient Safety.** Patients should not have to accept greater risks or uncertainties in using a follow-on product than an innovator's product.
- **Recognize Scientific Differences Between Drugs and Biologics.** Biologics are much more complex than small molecule chemical drugs.
- **Maintain the Physician-Patient Relationship.** The current state of science is not sufficient to establish interchangeability for complex follow-on biologics. Accordingly, Congress should ensure that patients are not given follow-on biologics unless expressly prescribed by a physician.
- **Preserve Incentives for Innovation.** Any statutory pathway for follow-on biologics must include a substantial data exclusivity period; must respect our intellectual property rights; and must provide adequate notice and process rights.
- **Ensure Transparent Regulatory Processes.** Any legislation must require FDA to follow a transparent and public process in determining data requirements for the approval of specific follow-on biologics.
- **Continue to Prioritize FDA Review and Approval of New Therapies and Cures.** Congress must ensure that workload associated with follow-on applications does not harm the FDA's ability to efficiently review new drugs and biologics.

First and foremost, patient safety must be assured. I trust that patient safety is a concern that we all share and that it will be a guiding concern for Congress as you consider a statutory pathway for follow-on biologics.

If follow-on biologics are to achieve the same standards of safety and efficacy as pioneer biotechnology products, then clinical trial evidence and data must be a fundamental requirement, and must be conducted on a product-by-product basis. The safety and effectiveness of a follow-on biologic simply cannot be assured without clinical testing, and in particular, immunogenicity testing, which is necessary to avoid putting patients at risk of adverse effects from immune reactions.

The stakes are too high to take the risk of moving too quickly and not following the science. In oncology, like in other therapeutic areas, we make our decisions on therapy selection based on clinical data and a deep understanding of both safety and efficacy: the risk to benefit ratio. Somewhat unique to oncology is the life-threatening nature of the illnesses we treat and the consequences of a wrong choice. For many patients, the first therapy is a chance for a cure that evaporates if the disease recurs, making it incurable.

Take for example the situation that women with Her2 positive breast cancer face every day. At diagnosis, women are treated with a balance of chemotherapy, including the biologic Herceptin, directed at the cancer protein along with surgery and radiation. For the majority of these women, their cancer will not return. Imagine a situation where a woman is treated with a follow-on biologic in this setting that has even a slightly different risk-to-benefit ratio, which allows her

cancer to return years later. The disease has now spread and her chances of survival are reduced significantly. What do we tell that woman and her family? That we never tested that follow-on biologic in humans, but we thought it was similar enough to Herceptin and relied on Herceptin's data to support its approval and to advocate for its use?

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

Differences between biologics and drugs

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 through extremely complicated and sensitive manufacturing processes.

As innovator companies' experience with respect to pioneer biotechnology products has shown, and as FDA has long emphasized through its regulation and guidance, small product or manufacturing differences in biologics can result in significant safety and/or effectiveness differences. 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 largely based upon strict control of the manufacturing process to minimize the likelihood of changes to safety and efficacy. Additional clinical testing is often required when substantial changes to the manufacturing process occur, and certainly the type of changes and differences in manufacturing necessary to producing a follow-on product would meet such a threshold.

While the ability to characterize biological products using physical, chemical, and biological testing has improved as science has advanced, current laboratory testing -- without testing in patients -- is still very far from sufficient to ensure that a follow-on biologic is without

differences from a reference product. These differences could adversely affect its safety or efficacy.

Furthermore, the methods used by innovators to demonstrate continued safety and effectiveness after a manufacturing process change are insufficient to demonstrate safety and effectiveness of a follow-on biologic made by a different manufacturer using a different process. 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. And clinical testing often reveals differences. This is important because by definition, the manufacture of a follow-on will necessarily involve very substantial manufacturing changes—a new cell line, a new facility, and a new process. These changes will result in a different product, and vastly increase the likelihood of clinically important differences, which can only be understood through clinical testing in humans.

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 the 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 the final, marketed reference product.

Additionally, optimal comparisons of "before change" and "after change" materials require an understanding of which parameters are key to ensuring the safety and efficacy of the molecule and what the best approaches are to assessing them. This understanding comes from years of working with the reference product, which 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 that sometimes helps address this question, the manufacturer of a new follow-on biologic will have limited experience with the molecule.

Thus, the ability of an innovator to make changes to its own manufacturing process, subject to the FDA's comparability guidelines, is simply not analogous to a follow-on company proving "comparability" when entirely different manufacturing processes are used. A manufacturer of a follow-on biologic will face significantly more limitations in demonstrating "comparability" than a manufacturer modifying its own process. When we make changes that might affect the clinical effects of a product, we 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?

Clinical trial evidence and data are fundamental for evaluating and demonstrating the safety and effectiveness of a follow-on biologic

In light of the limitations described above, and based on my experience, I firmly believe that there will always be a need for 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, and those determinations should be left to the FDA. Clinical trials will always be important to address questions such as immunogenicity, pharmacokinetics, and common adverse events under controlled conditions 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 for these products — those appropriately tested for safety and efficacy and those that are not.

There are many examples of how seemingly minor changes in a biologic's manufacturing process have resulted in significant changes in the product — changes that could only be detected 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 the course of demonstrating equivalence/similarity of biologics manufactured by different processes, it is important to consider that pharmacokinetics are not valid surrogates for clinical

effect for most biologics and, while pharmacodynamics endpoints may reflect biologic activity, they are usually unreliable surrogates for clinical efficacy and safety.

Our product, Raptiva (Efalizumab), was originally manufactured by XOMA, and was used in the Phase I/II trials and up to Phase III. When manufacturing was transferred to Genentech, manufacturing changes were made with the intent to preserve the distribution of molecular forms, which could be analogous to a follow-on product. Analytical and formulation differences expected to be inconsequential were observed. These differences were evaluated in extensive analytical and biological animal studies, and were found to have no effect on the pharmacokinetics. Further testing in a human bioequivalence study, however, demonstrated a significant difference between the XOMA and Genentech material. A second human bioequivalence study investigated the Genentech antibody in the XOMA and Genentech formulations and demonstrated bioequivalence, confirming that the formulation did not account for the difference.

Interestingly, based on the human PK data, once could imagine that administering ~70% of the dose of the Genentech antibody would have similar effects to the XOMA antibody. It did not. Because of the unpredictable nature of these observations, an additional Phase III study was performed to establish the safety and efficacy of the Genentech material.

Lessons learned here are that changes in the manufacturing process that we believed should not have a significant effect on the properties of the protein resulted in clear differences in pharmacokinetics. Furthermore, the higher drug exposure observed did not result in greater

efficacy. Given the complexity of the therapeutic proteins, the impact of changes in pharmacokinetics (and probably pharmacodynamics) on safety and efficacy cannot be reliable predicted. Thus, to establish therapeutic equivalence for follow-on biologics, it will be necessary to conduct controlled clinical trials to clear establish efficacy and safety profiles.

Immunogenicity testing is necessary to avoid putting patients at risk of adverse effects from immune reactions

Special attention should be given to the problem of immunogenicity: 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 biologics because (I) 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, 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.

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, J&J 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. Patients suffering this adverse event must undergo blood transfusions weekly for the remainder of their life. 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 that 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 examples I have given are just some of the cases in which immunogenicity concerns have arisen. Most biologics have some degree of immunogenicity. Immunogenicity levels can change with even slight changes in their manufacturing process and can have clinically important consequences. Scientifically, the only way to detect immunogenicity is through clinical testing.

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, which will be detected best or only through clinical testing. That is not to say that a full clinical testing program must be required for follow- on biologic products. Abbreviated clinical testing will sufficiently address key areas of uncertainty regarding safety and efficacy on a product-by-product basis, particularly where there exist good measures of desired effects (so called pharmacodynamic measures) and where a high degree of similarity is demonstrable. 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 foundation upon which any proposed regulatory pathway for the approval of follow-on biologics is created.

In addition, we believe that a follow-on product should be approved only for conditions for which the reference product is approved. For all the reasons discussed earlier, the safety, purity, and potency of the follow-on product for each indication must be supported independently, and attention must be paid to special safety risks (including possible immunogenicity) in different patient populations.

Interchangeability and substitutability: Congress should ensure that patients are not given follow-on biologics unless expressly prescribed by a physician

Given the complexity of biologics, the high potential for process differences to result in clinically meaningful product differences, and the limited ability to detect differences between a follow-on and reference biologic, a determination of comparability for a follow-on product is particularly challenging. Ensuring comparability of a follow-on biologic to a reference biologic with an acceptable degree of assurance will be made much more challenging 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. As a result, we believe that establishing the interchangeability of different products is not feasible, and therefore, is a decision that is only appropriately made by a treating physician.

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 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.

Given the risk of clinically important differences always at play and the possibility that substituting products would increase the risk of clinically important antigenicity, it is imprudent and potentially dangerous to allow the follow-on biologic to be considered "interchangeable" with its reference product.

The European Union (EU) 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 a few months ago, the French Parliament adopted legislation to prevent follow-on biologics from being treated in the same way as traditional generics, and banned the automatic substitution of one biologic medicine for another.

Given the current paradigm allowing for the substitutability of generic drugs with the innovator products they copy, a determination of interchangeability in this context would likely encourage the 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.html, 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.

In addition, it will be important for Congress to ensure that follow-on biologics are assigned a unique name -- one that has not be adopted for any protein manufactured by a different person – so that it is readily distinguishable from that of the innovator's version of the product. Assigning the same name to a product that is not the same would be confusing and misleading to patients, physicians, and pharmacists, could result in inadvertent substitution of the products, and would make it difficult to quickly trace and address adverse events that may be attributable to either the innovator or follow-on product.

Furthermore, if aspects of a follow-on biologic's 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 concern with one. Such a class effect is not in the best interest of patients or the industry generally, as overall confidence in biologics would be damaged.

Follow-on biologics should be properly evaluated through post-marketing surveillance and post-marketing clinical studies

All approved follow-on biologics will inevitably be associated with some risk that potential 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 may become apparent only after extensive use. To optimize patient safety and to control such risks, it is critical that the FDA not be limited in its ability to require 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.

After all of the attention Congress has given to the issue of drug safety evaluation, it would be intellectually inconsistent for this Committee to pass legislation that does not put forth specific provisions enabling adequate regulatory requirements for post-marketing safety surveillance programs and clinical studies of follow-on biologics. It would be equally problematic for any follow-on legislation to limit the ability of expert reviewers to negotiate for post-marketing clinical studies that could protect public safety.

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, a follow-on product must be as similar to the reference product on which it relies as can be achieved, in view of current scientific knowledge and technological capabilities. It must have the same route of administration, dosage form, and strength as the reference product.

In addition, 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.

Differences in Amino Acid Sequence

The amino acid sequence defines a protein. Even a minor difference creates a different (mutant) protein, and a product containing a mutant protein is a different product from the non-mutant form. Given the 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 AspB 10 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 AspB 10 was given to laboratory rats, it triggered the development of breast cancers.

When a change in an amino acid has occurred during premarket 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

"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.

Preserve incentives for innovation

In order to preserve incentives to research, develop and manufacture new innovative therapies and cures, as well as new indications for such products, any statutory pathway for follow-on biologics must also provide a substantial period of data exclusivity; must respect intellectual property and other legal rights; must provide adequate notice and process rights; must ensure a transparent statutory and regulatory process; and must continue to prioritize the review and approval of new therapies and cures. The importance of these measures is explained below.

Include substantial non-patent data exclusivity, during which time follow-on manufacturers could not rely on the FDA's prior approval of pioneer biologics to support approval of their own products. Such data exclusivity is necessary because a follow-on biologic may be similar enough to a pioneer biologic for regulatory approval purposes, but different enough to avoid infringing the innovator's patents. Thus, non-patent exclusivity is necessary to maintain effective market protection. Further, the fledgling nature of the biologics industry, its heavy dependence on access to significant amounts of high-cost public and private investment capital, and the high risks and costs involved in the development of new biologic medicines all warrant a substantial period of exclusivity.

Respect intellectual property and other legal rights. Follow-on biologic products should not be approved until after all statutory protections, including data exclusivity and patent protections, are no longer available for the approved pioneer product. Any follow-on biologics pathway should fully respect existing protections for trade secret and confidential commercial information, and not permit the use of such protected data for the purpose of approving follow on products. It also must not abrogate or limit constitutional or statutory rights of patent holders to protect against infringement.

Provide adequate notice and process rights. Any follow-on biologics regulatory pathway should ensure that patent challenges are litigated or otherwise resolved prior to marketing approval of the follow-on product, in order to protect the innovator's intellectual property rights and avoid confusion in the medical, patient, and payer communities. Further, any follow-on

biologics regulatory pathway should not create special patent litigation rules that favor follow-on biologics manufacturers.

Ensure transparent statutory and regulatory processes. Manufacturers of innovator products should be provided full and fair opportunities to engage Congress and other stakeholders in a meaningful public process. Establishing a balanced and rigorous statutory pathway for follow-on biologics requires deliberative evaluation of numerous complex scientific, legal, intellectual property and economic issues. Further, any such pathway must require that FDA follow a transparent and public process in determining data requirements for the approval of specific follow-on biologics.

Continue to prioritize FDA review and approval of new therapies and cures. Any applications for approval of follow-on biologics will raise novel and complex questions of science and law, requiring substantial time and additional resources to ensure a thorough regulatory review for safety, purity, and potency. In order to avoid slowing down the FDA's review and approval of new therapies and cures, many for currently untreatable and serious diseases, Congress must ensure that workload associated with these new applications does not harm the FDA's ability to efficiently review new drugs and biologics, and that new treatments continue to have the highest review priority.

As an oncologist and leader of a comprehensive oncology clinical development program, I am extremely concerned about the potential that limited or no data exclusivity would have on adjuvant – or early-stage – cancer drug development. It is in the adjuvant setting that we hope to

translate the breakthrough discoveries into cures for many of the incurable cancers that face us all. Limited data exclusivity in a follow-on biologics bill will lessen or eliminate the incentive successful cancer innovators have to continue investing in trials beyond the metastatic – or advanced stage - disease setting, since successful adjuvant trials are apt to return data suitable for an FDA submission late in the patent life of the product.

This is a significant issue because it could hinder research and development in the adjuvant setting. These studies are typically started only after positive Phase III trials in metastatic cancer and could take too long to be valuable and allow us to re-invest further in developing innovative therapies. Trials of adjuvant therapy are intended to catch the cancer at the time before it spreads, where our therapies could have the greatest impact for patients. Therefore, the need for randomized controlled trials is at its strongest in the adjuvant setting and requires a significant investment of time, money and human resources, as these trials are much larger in size. I will provide a couple of examples to help explain just how important this is to patients and our ability to potentially end the death sentence that cancer now represents.

In the case of our drug for HER2 positive breast cancer, Herceptin, we were only able to show that the drug could cut the recurrence of breast cancer in half in women with adjuvant HER2 positive disease years after completing a rigorous clinical trial and submission program in metastatic HER2 positive breast cancer. Prior to completing additional clinical studies of Herceptin, a diagnosis of HER2 positive breast cancer was among the most deadly a woman could receive. The approval for Herceptin in the adjuvant setting occurred 8 years after the original approval in the metastatic setting, and involved more than 3,500 women in multiple

randomized clinical trials. These trials can take easily take more than 5 years from inception to completion at the cost of hundreds of million dollars each, without any assurance of clinical success.

The Herceptin adjuvant program marked a first step in a major initiative to conduct studies of Genentech's targeted therapies in earlier stages of disease. This is again a critical issue when I think about the potential Avastin may have to treat patients with early-stage cancer. There are currently more than 300 clinical trials of Avastin underway today in more than 20 tumor types – including ovarian, brain and adjuvant colon cancer. Our investment in the robust Avastin development program is based on what we learned about the safety and efficacy of Avastin in metastatic colon, lung and breast cancer trials over the past decade.

Avastin is designed to interfere with the blood supply to a tumor by inhibiting VEGF, a protein that plays a critical role in angiogenesis, the formation of new blood vessels to the tumor. Genentech scientists identified the gene for VEGF more than 15 years ago and despite approval to treat patients with metastatic colon and advanced non-small cell lung cancer in the past 3 years, we are still years away from fully understanding how Avastin can best help patients with early-stage disease in the critical time before their cancer spreads.

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 is consistent with their

unique regulatory and health care framework. We should be able to leverage that work to have a frank and transparent scientific debate here in the United States, allowing us to develop a model which will be compatible with our own regulatory and health care system.

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. Instead, 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 inherent dangers of interchangeability.

The EMEA provided a broad regulatory framework, including the development of guidance documents, which outline the data requirements necessary to for the 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, which enumerate testing requirements on a product class-by- product class basis. 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; however, clinical testing, immunogenicity testing, and post-marketing

safety surveillance are all 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 proposed legislative pathways for follow-on biologics, you will pursue a 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 BIO and Genentech, that a transparent public process leveraging known scientific considerations will provide a framework and pathway for the approval of 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 will be realized for generations of patients to come. Again, I thank you for the opportunity to submit testimony for this hearing, and look forward to answering any questions you may have.