Science/Safety

1. What is immunogenicity? Why is immunogenicity a special concern for biologics and what are the risks to patients? Do immunogenicity risks vary depending on the type of biologic?

Immunogenicity is the ability of a biologic product to stimulate an immune system response in the body, prompting the formation of antibodies. Immunogenicity is particularly important in the context of 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 the body's own proteins as a means of survival. This means that our immune systems can be exquisitely sensitive to small differences in proteins. Thus, there is great potential for seemingly very minor differences 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 may inactivate the protein or cause it to be cleared from the body, and can result in a loss of efficacy and the progression of the disease. Some 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 to these therapies.

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 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, that the antibody binds to, potentially resulting in adverse and even life- threatening side effects. Some 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.

2. To what degree, if any, is immunogenicity testing necessary? Should immunogenicity testing be mandated by statute for all follow-on biologics (FOBs) or should the Food and Drug Administration (FDA) be given discretion to determine whether such studies, and what types of studies, are needed on a case-by-case basis?

Immunogencity testing including human clinical trials should be mandated by federal law. The degree of mmunogenicity can change with even slight changes in their manufacturing process and can have clinically important consequences. Scientifically, the only way to detect the degree of immunogenicity is through clinical testing. Given that follow on biologics are, by definition, different than the reference product, patient safety concerns necessitate that immunogenicity testing be conducted.

3. Has FDA exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes? Should immunogenicity testing for manufacturing changes be mandated by statute, or should FDA be given discretion to determine whether such testing is necessary?

In our experience, the FDA has appropriately exercised its discretion regarding whether and what kind of testing to require when manufacturing changes are made. That said, 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. Specifically, 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.

4. Should FOB applicants have to provide evidence of similarity, safety, and effectiveness of each indication separately or can evidence for one indication be extrapolated to another?

FOB applicants should be required to provide evidence of similarity, safety and efficacy as to each indication for which the reference product is approved. In addition, we believe that a follow-on product should be approved only for conditions for which the reference product is approved. For reasons outlined in our attached testimony from May 2, 2007, 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. The FDA requires innovators to also seek additional approval for new indications. This is because the FDA understands that biologics may not function the same for other diseases or in different patient populations, and as such, additional testing is required to ensure the product's continued safety and efficacy for those indications. Therefore, for a follow on product to truly be a follow-on and to ensure it's safety for use by patients, it must be required to prove safety and efficacy for all indications for which the reference product has been approved.

5. Under the Food and Drug Administration Amendments Act of 2007, Congress established new authorities for FDA to enforce drug safety. How should the new post-market authorities enacted in this legislation be applied to FOBs? Are post-market studies always needed for FOBs? Are there situations in which FOB applicants will need to conduct post-market studies that are different from those that have been required and/or requested for the reference product?

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.

Given the Congress' attention to post-marketing requirements in the FDA Amendments Act of 2007 (FDAAA), it would be intellectually inconsistent to enact a FOBs pathway 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.

6. Should non-interchangeable FOBs be required by statute to have different non-proprietary names from the reference product? What should the standard be for interchangeable FOBs? What are the advantages and disadvantages of requiring different non-proprietary names, including any affect on patient safety? What alternatives are available?

Yes, it is 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 and from each other. 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 to a particular 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.

7. Is it important that an innovator and an FOB have the same mechanism of action? Why or why not? If the mechanism of action of the reference product is unknown, should the FOB applicant be required to determine the mechanism of action and ensure that both products share the same one? Why or why not?

Yes, a follow on product should be required to have the same mechanism of action. In the absence of such, the product should not be considered as a follow on to the reference product, but rather, should be reviewed as a new and separate product under a full BLA.

8. How much variability in chemical structure is there in individual brand biologics: (1) batch-to-batch, and (2) as a result of manufacturing changes? What are the implications, if any, for FOBs testing requirements, naming, and interchangeability?

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 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?

9. Should human clinical trials be mandated by statute for all FOBs or should FDA be given discretion whether such trials are needed on a case-by-case basis? Would not requiring human clinical studies of FOBs result in these products having a more difficult time reaching market acceptance? Why or why not?

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 largely 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. New legislation should not cause patients to take a biologic that had not been appropriately tested in humans; the risks are too high. 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.

10. What studies have been required for past approvals of protein products under section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA)? Have any been approved without clinical trials?

N/A

11. Omnitrope is approved in the U.S. (albeit as a 505(b)(2)) and in Europe (as the first biosimilar).

    a. Have patients experienced any problems?

b. Have patients been switched to Omnitrope from other recombinant human growth hormone products?

c. If the answer to part b is yes, how are payers handling the availability of this comparable product?

N/A

Regulatory/Administrative

1. Some believe Section 505 of the FFDCA provides a regulatory pathway for approval of biosimilars for reference products approved under Section 505. Should a newly created biosimilar regulatory approval process include all biologics approved under the FFDCA as well as those regulated under the Public Health Service Act?

Yes. There is no policy rationale for maintaining two separate approval processes for the approval of follow on biologics. As such, follow on companies that seek approval of a biologic approved as a drug under the FDCA should also be required to meet the requirements of any new legislation.

2. The current statute gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial. Do you think this statutory discretion has been appropriate or adequate? What has been its effect on patient safety?

Please see answer to Science/Safety question #3 .

3. What FDA office should review FOBs?

The same office that reviewed the reference product should review the application for the follow-on product, as that office will have the necessary expertise.

4. What standards are required to assure sufficient similarity between the FOB and the reference product? Is the requirement that the FOB be "highly similar" to the reference adequate or should an applicant be required to establish that the FOB is "as similar as scientifically as possible"? How would FDA assess these requirements?

Since it is not possible to make two biologic products identical, follow-on biologics will, by definition, be 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.

5. Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue and permit public comment on product-specific guidance before submission of applications? What are the advantages and disadvantages? How long will it take to put a regulatory framework in place, including new regulations and guidances for FOBs?

Yes, the FDA should be required to either promulgate regulations or issue scientific guidance documents outlining the review requirements of each class of products. The FDA issues guidance documents on a regular basis and so should not represent any unique regulatory or administrative burdens.

6. How much in additional appropriations or user fees would FDA need to implement a generic biologics program? What proportion of resources should come from user fees? How would that relate to the user fees that are assessed for traditional drugs and/or biologics?

N/A

Interchangeability

1. Does current science permit an assessment of interchangeability (substitutability) for any biologics at this time? What is the likelihood that interchangeability assessments for some or all biologics will be possible in the future, and in what period?

The assessments of "interchangeability" and "substitutability" are two different issues. Interchangeability refers to different products that can be prescribed, based on the judgment of the physician, to treat the same medical condition. This is sometimes referred to as "therapeutic substitution". Physicians have this authority now and presumably would continue to have it under follow-on biologics legislation. Substitutability, on the other hand, would permit pharmacists to "substitute" a generic or follow-on product for the one prescribed by the doctor, sometimes referred to as "generic substitution," without first seeking approval from the prescribing physician.

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 "substitutable" with its reference product. As we describe fully in our attached testimony before the House Energy & Commerce Health Subcommittee on May 2, 2007, 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, make the determination of comparability for a follow-on product 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 substitutability 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.

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 "substitutability" 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. To date, at least 11 European countries have adopted law to prevent the automatic substitution of biosimilar products for the reference product.

Furthermore, given the current paradigm within the US of allowing for the substitutability of generic drugs with the innovator products they copy, a determination of substitutability in this context would likely encourage the substitution of one product for another. In September 2006, the FDA expressed concerns about substitution of one biologic medicine for another: "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).

Even if products have a determination of comparability but not substitutability, substitution could occur, potentially unbeknownst to the prescribing physician or patient and potentially with adverse health outcomes.

2. In general terms, what types of testing or data would be necessary to establish that two biologics are interchangeable?

N/A

3. How should product-specific requirements for demonstrating interchangeability be established? Should the statute prohibit interchangeability assessments or give FDA the authority to determine interchangeability as science permits? Please explain your answer.

Interchangeability, or "therapeutic substitution", is properly within the realm of the prescribing physician. We believe there are inherent risks with allowing substitutability, or "generic substitution", of follow on biologics and it should only be permitted when/if the FDA believes there is sufficient scientific rationale for making such a finding.

4. Should there be product specific guidances, with opportunity for public comment, on establishing interchangeability before submission of applications? What are the advantages and disadvantages?

Again, interchangeability, or "therapeutic substitution" is a determination for the prescribing physician to make. To the extent the FDA believes that findings of substitutability, or "generic substitution" are scientifically feasible, they should be required to publish guidance outlining the standards and rationale before making such a finding.

5. What are the potential risks to patients from interchangeability of one biologic for another? If FDA finds two biologics interchangeable, should physicians, pharmacists, and patients feel comfortable with substitution by pharmacists? Why or why not? How would interchangeability affect patient access to biologics?

Please see answer to question #1.

6. How would interchangeability affect competition in the market place, and/or reimbursement by health plans? Will it affect the costs of biopharmaceuticals?

   N/A

Patents

1. In your view, how long is the current effective patent term for pharmaceuticals? Specifically, how long on average are drugs marketed under patent protection following FDA approval?

The effective patent term (the period of patent life left after a new drug has been approved for marketing) can vary widely depending on the circumstances of the drug involved and the nature of any patent rights that may exist for the drug product or its approved uses. For example, a new drug that is based on a new chemical compound that has never been approved often faces a longer period for regulatory review than an application seeking approval of a new use of a previously approved drug product. The effective patent term for such products often will be short due to two factors; namely, that the chemical compound patent will have been filed early in the research and development process of the drug, and because the long regulatory review period will consume a significant portion of the overall patent term. While some of that term can be restored, there often is only a short period of patent term remaining in these situations.

New use patents can be secured for new indications approved for an existing drug product. However, these patent rights are often limited in scope, except where the new use is a dramatic departure from the originally approved indication. In general, the more closely the indications are related, the less likely independent patent rights will be available to protect the new use.

Unfortunately, there are no readily available statistics measuring effective patent term using the parameters of this question. One source of information is the average patent term restoration period granted for patents. Reports from the PTO indicate that the average period of patent term restoration is 2.3 years. Since one of the caps on the length of a patent term restoration is the 14 year effective term limit, one can assume that some percentage of new drugs reach this period of effective patent term. Another source is a report of the Congressional Research Service that estimated that new drug products are marketed without generic competition for approximately 11 years following approval of the new drug application. See, "Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act") (updated December 18, 2000)." While both of these figures provide an incomplete picture, they do offer some insights into the average period during which new drug products are marketed under patent protection.

2. The Hatch/Waxman Act restored innovator patents up to 14 years, and further provided manufacturers with 5 years of data exclusivity. Is this a good model for biologic manufacturers? What lessons can we learn from the Hatch-Waxman Act, and apply towards Congress's discussion about FOBs?

Because follow-on products would not be identical to innovator products, the Hatch-Waxman Act - which restored innovator patents up to 14 years and provided five years of data exclusivity - is not a good model for biologic manufacturers. The regulatory approval setting for follow-on biologics ("FOBs") is fundamentally different than regulation of small molecules under the Hatch-Waxman Act and requires a much longer data exclusivity period than five years. Under the Hatch-Waxman Act, generic drugs generally must be identical to the reference product and will likely fall under the reference product's patents. By contrast, FOBs will be similar, but not identical, to the reference product. As FOBs may differ from the reference product, FOBs are less likely to be covered by reference product patents than generic drugs under the Hatch-Waxman Act. This means that often a FOB will be able to avoid the patent rights of the innovator that are limited to the specific innovator biological product that serves as the basis of the FOB request for approval.

A longer data exclusivity period is required to compensate for the increased frequency of situations where no patent protection will be available. Without a sufficient period of data exclusivity, the risks to innovators will increase substantially and their ability to bring new products to the market will be reduced.

Additionally, the patent restoration and data exclusivity periods under the Hatch-Waxman Act run consecutively, and the data exclusivity period is often subsumed in the patent term rendering it meaningless. The lesson learned from the Hatch-Waxman Act is that patent term restoration and data exclusivity are independently important, and both periods must be sufficiently strong to encourage innovation.

3. Please explain if patents on biotech medicines will provide meaningful protection of intellectual property if a pathway is created to allow for the regulatory approval of FOBs? How do patents on biotechnological medicines compare or differ in the value they offer to traditional small-molecule drugs, if an FOB's pathway requires only that the FOB be highly similar to the reference product?

A follow-on biologics pathway that would require the FOB to be only highly similar to the reference product would render patents on biotechnological products less valuable than patents on small molecule drugs. Under the regulatory scheme for small molecules, the generic drug must generally be identical to the reference product. Thus, a company that develops a reference product and obtains a patent on that product can be certain that the patents will provide adequate protection against generic products. But if FOBs are allowed to differ in structure or other characteristics from the reference product, yet still be considered highly similar, any patents that cover the reference product may not cover the FOB variant. Accordingly, the value of each patent related to the reference product is less certain.

Generally speaking, patent protection has the capability to protect biotech medicines. However, patentability standards have evolved over the last 20 years to

provide a limited scope of protection for biotechnology products. In particular, patent coverage is generally limited to compounds that are known and adequately described in the patent application. Biotechnology is considered an unpredictable art because the effects of even a minor change in a biological product are often unknown. This unpredictability has the effect of limiting the ability of patent applicants to secure broad coverage for their patents that extends to molecules that differ even in minor ways relative to a protein that was subjected to experimental testing. Thus, it is difficult for the owner of a biotechnology product to obtain broad patent coverage that can protect against the possible range of FOBs that may be approvable under the proposed regulatory pathway. The inherent uncertainty regarding the scope of patent protection for biological products dilutes the patent system as an incentive mechanism for the development of biologics.

4. What procedures, if any, should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims by a biosimilar company and to ensure timely resolution of legal disputes?

All potential patent conflicts should be identified early in the process, all parties to the patents should be notified in a timely manner, and resolution to those conflicts should be completed prior to the expiration of data exclusivity.

Unlike small molecules, biological products are essentially defined by their manufacturing process. Furthermore, patents that are relevant to a particular biological product are often held by entities other than the owner of the reference product, such as small biotech companies and universities. Any FOB legislation should ensure that all relevant patents, including manufacturing patents and those patents held by third parties, are identified to the FOB applicant, before the FOB product is approved and placed on the market. A procedure in which interested patent owners provide patent information to the FOB applicant and the FOB applicant provides confidential information regarding the FOB product to the patent owners is essential to identifying and resolving patent infringement issues efficiently before the FOB obtains approval. Additionally, the patent process contained in any FOB legislation should provide the parties with an opportunity to execute a patent license if appropriate to minimize unnecessary patent disputes.

5. If patent issues are to be addressed in a statute, how should we balance the interests of third-party patent holders and the reference product sponsor?

Both the third-party patent holder and the reference product sponsor require sufficient notice of applications for follow-on products that might implicate their patents. A process should be established to promptly notify all interested parties of the application and resolve any potential disputes before the follow-on product reaches the market.

Third party patents play an important role with respect to biological products, particularly with respect to manufacturing and platform technologies. Patents represent an important property right around which many small biotech companies are built. Accordingly, it is essential to have third parties participate in the FOB process to protect their interests. Moreover, the holder of the reference product cannot be expected to act on behalf of every interested third party. In many cases, patents that relate to a FOB product may not be relevant to the innovator product, and vice versa. In addition, particularly with respect to patents that are non-exclusively licensed or otherwise not in the control of the reference product holder, the third party is the only party who could take legal action against an FOB applicant. Finally, the holder of the reference product should not have to bear the liability that would accompany the requirement of having to act on behalf of third parties.

6. Should an FOB statute require FDA to administer patent listing and notification provisions as Hatch-Waxman does? Has this process been an appropriate and efficient use of FDA's resources and expertise? Why or why not? Can appropriate notification be accomplished through an alternative process that does not enlist FDA resources?

An FOB statute should not require FDA to administer patent listing and notification provisions as is done under the current Hatch-Waxman Act. Any FOB legislation should seek to minimize the burdens on the FDA. The FDA has consistently stated that it has no patent expertise and views patent listing as a purely administrative function. Due to the increased number of patents involved with respect to biological products, an FDA compilation of patent listings would be complex and burdensome to manage. As there is no technical need for FDA to be involved in a patent identification process, it would be more viable and efficient for the legislation to provide for a direct exchange of patent information between patent owners and FOB applicants.

While the FDA should not be burdened with a patent notification process, there would be value in the FDA maintaining public information concerning the period of regulatory exclusivity awarded to biological products. Such a function is more clearly its purview, and would have value for the public.

Incentives/Exclusivity/Investment

1. Should reference product manufacturers be given a period of exclusive marketing in addition to the patent-term restoration already provided to them under Hatch-Waxman? If yes, how much is necessary to provide adequate incentives for innovation without unnecessarily delaying competition?

A period of data, not market, exclusivity is essential. As mentioned above, follow-on products will not be identical to innovator products and thus the original product may not be sufficiently protected by its patents. A period of data exclusivity that may run concurrently with the relevant patents, if any, would ensure the innovator has adequate time to recoup the research and development investment that went into creating and developing the product, which usually takes 10-15 years before the product first becomes available to patients.

The data exclusivity provisions should ensure 14 years of exclusivity for innovator products in order to provide adequate incentives for innovators to do adjuvant studies of oncology products approved for metastatic oncology indications. Study for use of an oncology product in the adjuvant setting can take years following approval for use of the product in the metastatic setting and a sufficient period of exclusivity is necessary to allow this important research.

2. What types of assessments have been conducted to determine the minimum term of exclusivity that will enable a robust industry for discovery and development of biologics?

The Center for the Study of Drug Development at Tufts University has found that the average innovator biologic costs around $1.1 billion to discover and bring to market. Data exclusivity is necessary because a follow on biologic may be similar enough to an innovator biologic for regulatory approval purposes, but different enough to avoid infringing the innovator's patents as discussed in question 1. The CSDD did its first pharmaceutical cost analysis in 1979, so it is my assumption that the drafters of Hatch-Waxman had similar research resources to those available to the Committee currently.

The real reason to have robust data exclusivity is to provide an incentive for innovators to conduct long, expensive and risky trials for adjuvant oncology indications, which can only occur following metastatic approval. Dr. David Schenkein discussed this issue in his May 2, 2007 testimony before the Committee. The example he provided was Herceptin for Breast Cancer. Herceptin was shown to cut the recurrence of breast cancer in half in women with adjuvant HER2 positive disease. The trials that proved this result included 3500 patients, as opposed to the 464 in the original metastatic trials. The adjuvant approval came 8 years after the original approval and was stopped early due to the robustness of the data. If the trial had been open for the planned 5 years, Herceptin would have approved in the

adjuvant setting 10 years after its original approval. The congress needs to provide incentives for companies to complete these trials that can improve public health.

Many biotechnology innovations are in the area of oncology and some of the greatest successes are achieved when products can be used in the adjuvant setting. It is important to create an environment, including a robust period of data exclusivity, that maximizes innovation through adjuvant trials.

3. How should exclusivity for modifications to approved products be addressed?

The Public Health Service Act and the FDA have made it quite clear to innovators when a clinical trial is required to modify a currently marketed product. If the question is directed to new BLAs for a second-generation product, the new product has its own BLA and dataset and that new data must have its own data exclusivity. To do otherwise would kill any incentive for a company that likely knows the most about the science underlying a disease state or cascade the opportunity to take advantage of further knowledge to innovate on a better bind to a receptor site or other means of inhibiting the disease. How would the committee craft a statutory rule defining what would be a second-generation product and what would be sufficiently different to be a different innovative product in a disease category? To use anything other than a new BLA standard would effectively deny patients improved therapies for diseases.

4. What benefits do innovator firms obtain from data exclusivity, and how is this protection different from patent protection?

As discussed above, data exclusivity is necessary because a follow on biologic may be similar enough to an innovator product for regulatory approval purposes, but different enough to avoid infringing the innovator's patents. In order to have innovation in biotechnology, it is important to provide robust data exclusivity. Note that Genentech is not asking for market exclusivity; if a competitor believes they have a product that does not infringe our products and wins approval of a BLA for their product, they are welcome to the competition in the marketplace and patent court.

5. Do you think biologics should receive a different period of data exclusivity than drugs? Why or why not?

Biologics should be treated differently than drugs because, unlike drugs, follow-on biologics will only be similar – not identical – to the innovator product. Because of this important difference, patents will not sufficiently protect innovator biologics and a robust period of data exclusivity must be established.

Our research and development priorities primarily focus on "breakthrough" biologics for which there is little or no existing research and development, but for which there is a critical unmet need. Breakthrough and innovative biologics are inherently risky, and successes are low, meaning fewer revenue earning products

are generated. The potential for failure, as well as the increased expense in developing breakthrough products, makes access to R&D funds crucial for biotechnology companies. We are financially dependent upon revenues from the sales of the products we develop. Our internal allocation of financial resources and the direction of our innovative R&D efforts are determined in large part by the revenue anticipated from the sales of these commercial products. To the extent that follow-on biologics impact our revenue stream, our investment in innovative R&D will also be directly impacted.

6. What policy considerations justify that patent protections be the principal form of intellectual property protection for biologics and drugs?

For many years patents have been the principal form of intellectual property protection for dugs and biologics. There is a well-established system of awarding, administering and understanding patents that has provided certainty both for innovators and those seeking to challenge innovative products.

The Hatch-Waxman law implemented a method of pharmaceutical cost control in the US that promotes innovation through patent protection without price controls and the rapid introduction of generics once the patent expires. While other countries have implemented different system to control drug costs, the US is now the most innovative pharmaceutical market in the world and the most robust generic market in the world.

7. If a follow-on biologics pathway was created without additional incentives—beyond existing patent protections—for continued innovation, how would innovation be affected either positively or negatively? What additional incentives, if any, would be necessary to support continued research and innovation, including at American universities?

Existing patent protections continue innovation, but a system must be devised to protect the data in the innovator's BLA submission from use by a follow on. As discussed earlier, data exclusivity is necessary because a follow on, unlike a generic, may be similar enough to an innovator biologic for regulatory purposes to gain approval, but different enough to avoid infringing the innovator's product patents. Thus, data exclusivity is essential to have a positive effect on future innovation. A patent litigation system that ensures that all patents, including those held by third-parties, are litigated and decided prior to the expiration of the data exclusivity for each product, will support continued research and development while avoiding needless delays in FOB product introduction by court proceedings.

Genentech currently plans to spend about 20 percent of its revenues on R&D in the short-, mid- and long-term horizon. This substantial investment (roughly $34.2 billion over the next 10 years) is needed in order to realize the full potential of our science and of our strong product pipeline. If a follow-on biologics pathway is

created without additional incentives for continued innovation, innovation would be negatively impacted due to the fact that spending is reliant on a revenue base to support it. If our revenue base is negatively impacted in ways that we do not currently project, then R&D spend will decrease by a directly proportional amount.

Economic Impact

1. How much savings would a generic biologics pathway create and in what period (taking into account the time it will take to implement any new law, and the time needed by manufacturers to develop products and submit applications)? Please describe the evidence on which you base your answer.

First, there is no such thing as a generic biologic. Manufacturers of biologics that do not have the original cell line and product process science "recipe" for the product cannot make generic, or duplicate, biologics. They may be "highly similar" or "comparable", but they are not "same" under the FD&C law. If the questions is how much can follow on biologics save, CBO will provide the ultimate unbiased answer. Genentech urges the Committee to ask CBO to study the question and give the score of the bills introduced on the subject. There are studies done by those who replicate the CBO process and studies that create their own process, but CBO is the proper place for the Committee to ask this question.

2. Can you provide an estimate of the amount of money your agency/company will spend on biological products over the next 10 years, in absolute dollars, and as a percentage of total program/plan spending? If FOBs, approved by FDA as comparable to the brand name product, were available, what is your estimate for the cost of the reference product and the follow-on product?

As stated above, Genentech currently plans to spend about 20 percent of its revenues on R&D in the short-, mid- and long-term horizon. This substantial investment (roughly $34.2 billion over the next 10 years) is needed in order to realize the full potential of our science and of our strong product pipeline. If a follow-on biologics pathway is created without additional incentives for continued innovation, innovation would be negatively impacted due to the fact that spending is reliant on a revenue base to support it. If our revenue base is negatively impacted in ways that we do not currently project, then R&D spend may well decrease by a proportional amount.

3. What implications would a follow-on biologics pathway have on U.S. economic competitiveness and leadership in protection of intellectual property rights?

The innovator biotechnology industry was born in the U.S. and has thrived in an environment of robust patent protections, because they are required to entice the risky, long term investments that are necessary. The United States is the world's leader in biotechnology. A FOB system that does not provide for robust protections through data exclusivity could endanger investment in the industry and threaten the advantages the biotechnology industry provides the US in a competitive global environment as well as the U.S. leadership in biotechnology.

4. What implications does the treatment of patents in the context of a follow-on biologics approval pathway have for the future of biotechnological innovation?

If innovators have incentives to create new therapies and the investment necessary to carry them through to patients, the industry can prosper. Patents alone cannot provide the protection required, as mentioned above. Since follow on biologics can be similar enough to gain regulatory approval and possibly different enough to avoid infringement, a robust data exclusivity period must be created in the legislation.

5. If a follow-on biologics pathway was created without ample incentives for innovators to continue to innovate, what would the effect be for future research, current clinical programs, and universities?

As mentioned above, Genentech depends on current profits to fund research and development of product pipeline. This pipeline includes significant new science that could affect public health. Lowering the level of research and development spending as a result of lower product sales due to an inappropriate level of incentives could hamper the development of new therapies. The base science for these new therapies will come from discoveries at Genentech and its academic and commercial partners, many of whom are small companies. Lowering incentives could shelve or slow development of these therapies, delaying and possibly denying patients potential therapies that can treat or cure their conditions.

European Model (abbreviated approval pathway)

N/A

1. The European Union (EU) regulatory system for biosimilars requires the development of product-specific guidances which detail the standard for approval that would need to be met by a biosimilar in a defined product class. Do you think these guidances would provide similar benefits to industry, healthcare providers, and patients in the U.S.?

2. Legislation passed by the European Parliament encourages innovation by providing 10 years of market exclusivity, extendable to 11 years for select new indications of use, for innovator biologics, thereby preventing the introduction of FOBs during that period. Should the U.S. be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?

3. If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, what could the potential effect be on U.S. competitiveness?

4. To what extent do you agree or disagree with the EU's current model when it comes to access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for the approval of a new product? What are the advantages and disadvantages of the EU's model? Are there other models that the U.S. can examine? If yes, what are the strengths and weaknesses of their models?

5. FOBs are now approved in Europe, and FDA has approved a number of follow-on protein products under the FFDCA. Have these shown any problems with respect to safety or efficacy? In what ways are these different from any safety problems seen with brand products?