MILLENNIUM

Millennium Pharmaceuticals, Inc.
1401 H Street, N.W., Suite 200
Washington, D.C. 20005
202.289.6598
www.millennium.com

May 2, 2008

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Room 316 Ford House Office Building
Washington, D.C. 20515

The Honorable Nathan Deal
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Room 316 Ford House Office Building
Washington, D.C. 20515

Dear Chairman Pallone and Ranking Member Deal:

We appreciate the time and effort that you and the Subcommittee are investing to evaluate the complex issues associated with the creation of a follow-on biologic ("FOB") approval pathway. Millennium shares your commitment to ensuring that critical and life-saving therapies are available to Americans. We are pleased to provide our responses to the questions posed in your letter dated April 3, 2008.

Millennium, a leading biopharmaceutical company based in Cambridge, Massachusetts, markets VELCADE®, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Millennium research, development and commercialization activities are focused in two therapeutic areas: oncology and inflammation. By applying our knowledge of the human genome, understanding of disease mechanism and industrialized drug discovery platform, Millennium is developing an exciting pipeline of innovative product candidates, including biologics.

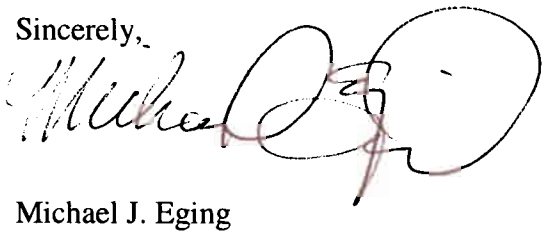
Our mission is to convert our scientific and technical expertise into important advances for patients. It is our experience that bringing a safe and effective biologic to market requires significant investments of both time and capital. The ability of companies, particularly small and emerging biotechnology firms, to develop critical new therapies for patients hinges on their ability to remain viable, while performing the research and testing necessary to demonstrate the safety and effectiveness of a new medicine. In our case, the successful commercialization of one product is fueling our efforts to develop additional novel treatments for patients with serious health care needs. Preserving incentives for innovation helps ensure that therapies will be developed for those patients, who currently have little or no treatment options, and that advances will

continue to enhance existing treatment options – often improving and extending the lives of patients.

We support the Subcommittee's efforts to develop legislation that strikes an appropriate balance between encouraging biopharmaceutical innovation and fostering a competitive biologics marketplace. We believe our responses to the Subcommittee's questions explain and provide greater detail on how best to strike this balance. We would be happy to answer any further questions the Subcommittee may have.

Thank you again for the opportunity to comment on this critically important issue.

Sincerely,



Michael J. Eging
Vice President, Government Relations and
Public Policy

Responses to Questions on Follow-On Biologics from the House Energy & Commerce Subcommittee on Health

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 or likelihood to stimulate an immune response in a person once a biologic is administered. Small molecule (*i.e.*, chemically synthesized) drugs do not generally induce this type of response. Many biologics, because they "replicate" a naturally occurring protein in the human body, can induce antibodies in patients. Induction of antibodies can cause no effect, or it can impact pharmacokinetics (how the biologic is distributed and cleared in and by the body), pharmacodynamics (the effect that the molecule has on the body), safety or efficacy. Effects can be manifested as a neutralizing biologic response which can impact the clinical response in humans or the antibodies can cross-react with endogenous (naturally occurring) proteins and induce adverse symptoms.

Immune responses may be serious or life-threatening; therefore, it is critical that this issue be addressed for biologics both in terms of the innovator product, but even more importantly with a so-called follow-on biologic or "FOB". Immunogenicity risks can vary depending on the protein. Factors that can influence the immunogenicity of proteins are the molecular structure (caused by differences in the amino acid sequence or "genetic instructions" used to trigger production of the product), including glycosylation (the addition of "sugars" intended to extend the dosing within the body), and process and product impurities, including aggregates and degradants. Immunogenicity can also be influenced by patient-related and disease-related factors. It is not yet possible fully to predict induction of antibodies and the effect based on only pre-clinical, *i.e.*, non-human, evaluation studies.

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?*

Immune responses can be serious, life-threatening and can adversely affect efficacy; therefore, it is critical that immunogenicity testing in humans be conducted. The ability to predict whether a protein product will induce an immunogenic response, particularly the more complex proteins, is limited. The FOB manufacturer is using an entirely different cell line from the cell line used to manufacture the innovator product. This may result in differentiation between the FOB and the innovator product that may not be detected analytically. Additionally, the FOB manufacturer will not have knowledge of the innovator's complex yet precise manufacturing process steps. Any differences in the manufacturing process may introduce changes to product or process impurity profiles

which may impact the immunogenic potential of the FOB. Animal studies are helpful in elucidating potential differences in product immunogenicity but are not sufficient. Therefore, some degree of human clinical assessment of an FOB's immunogenic potential should normally be required.

We encourage the Committee to approve legislation that gives FDA the discretion to determine what studies will be required to permit approval of an FOB application. However, we cannot support legislation providing FDA with such discretion absent the requirement that FDA develop, through public notice and comment processes, product-class specific guidance, which would address the type and scope of studies needed to approve an FOB application. We believe such guidance requirements will best safeguard the public's health, by allowing for the continuing evolution of this science, while also ensuring that all FOB applications include the data necessary to ensure the product is safe and effective, and also does not result in adverse immune response effects.

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 the innovator context, FDA has demonstrated appropriate discretion in its requirements for immunogenicity testing for manufacturing changes where all process steps are known. Whether a manufacturing change requires immunogenicity testing depends on many factors, such as the nature of the changes, the product, the indication, and the human clinical and manufacturing experience, among many other considerations. It is important, however, to recognize that the manufacturer of an FOB will lack this intimate knowledge of the manufacturing processes used by the innovator, which creates a fundamental difference between manufacturing changes implemented by an innovator and those implemented by an FOB manufacturer.

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?*

An innovator company is required to provide safety and efficacy data for each indication that is approved for its product. The FOB applicant must also be required to supply evidence of similarity, safety and effectiveness to support each indication. The extent of this evidence would depend on the similarities and the nature of the indications. There are two primary reasons that FOB applicants should perform separate studies to support the safety and efficacy of the FOB for the treatment of each disease.

First, an FOB applicant can never be identical to the innovator's product because a different process must necessarily be used to manufacture the protein, *i.e.* different cell line, raw materials, manufacturing process, test methods, reference materials, specifications, container/closure system and manufacturing and testing facilities. Therefore, it is impossible for the FOB to be identical to the innovator product, and the biological characteristics of the FOB may ultimately differ from the innovator product. As a result, the FOB may differ from the innovator product with respect to safety and/or

efficacy of the two products, depending on the indication.

Second, in some cases, the mechanism of action of the innovator product is not known or not fully understood. Sometimes the primary mechanism of action is known, but there may be secondary mechanisms of action that may vary across diseases. Additionally, safety issues may vary depending upon characteristics of the patient. This may include the type of disease or the administration of concomitant medications, among other patient-specific variables.

For these reasons, FOB applicants must demonstrate safety and effectiveness of their products for each intended indication.

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?*

Title IX of the Food and Drug Amendments Act of 2007 ("FDAAA") provided authorities for FDA to enforce completion of Phase IV (post-market) studies and to require a risk evaluation and mitigation strategy ("REMS") either before or post-approval. Further, Section 901(b) of the FDAAA, which amends Section 505 of the Federal Food Drug and Cosmetic Act ("FFDCA"), specifies that drugs approved under the abbreviated approval requirements of 505(j) are subject to limited obligations under the new REMS requirement.

The enhanced safety authorities provided to FDA in the FDAAA are intended to address concerns that FDA had inadequate authority to require completion of studies necessary to ensure the safe use of approved drugs. The enhanced powers are largely discretionary on the part of FDA. Understanding the purpose and discretionary nature of the authority, it seems appropriate to extend the authority to oversight and regulation of FOBs. Unlike drugs approved under 505(j), sponsors of FOBs will be unable to show that the FOB is structurally identical to the reference listed biologic. For this reason, it is clearly appropriate to require full compliance with the REMS, when deemed necessary by FDA.

It is not clear that post-market studies may always be necessary. This should be determined on a case-by-case basis, as is currently done for innovator drugs.

The nature of the post-market studies may be the same or different from studies performed on the reference listed drug. Studies performed to further demonstrate comparability to the reference biologic may entail a reproduction of the same study to assess similarity of results. If there are additional, potentially different, safety questions or concerns associated with the FOB, it may be necessary to perform different studies, pre-market or post-market, than were required or performed for the reference biologic.

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?*

A non-interchangeable FOB should be required to have a different non-proprietary name from the reference product. Differentiation of the products by name will help ensure that a physician is prescribing the product most appropriate for a particular patient. Name differentiation will also help to ensure that a pharmacist is not inadvertently substituting a product that may not provide the same clinical result in humans as the same-named brand product. Requiring unique non-proprietary names for FOBs will also avoid confusion among patients.

Interchangeable FOBs should be expected to produce the same clinical result in humans as the reference product and should not present additional safety risks and/or result in diminished efficacy if a patient changes between products. In a simplistic sense, products having the same name should be expected to be "the same" in all relevant respects. In the case of FOBs, this would mean that the FOB provides the same benefits to the patient as the brand product, with no additional risks of adverse effects or immune responses, particularly if the patient switches between products.

We recommend that each biologic product have a unique non-proprietary name. An alternative would be to assign a suffix to all FOBs, where the core of the non-proprietary name is determined as under the current scheme and the suffix designates the product as an FOB, regardless of whether it is interchangeable.

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?*

If the primary mechanism of action of an innovator product is known, then the FOB applicant should demonstrate the same mechanism of action in order to rely on the findings of safety and efficacy for the approved product. Having the same mechanism of action is one step in demonstrating that the FOB is sufficiently similar with respect to the structure, function and clinical results in humans of the innovator product. Also, the mechanism of action for some biologics is based on a specific type of interaction with a target, *e.g.*, binding to a receptor. Some innovator products are very specific in the type of interaction or target, such as binding only to a specific subtype of a receptor. Differences between the FOB and the innovator product, in the selectivity of a target and the specific interaction that results, may lead to differences in the safety or efficacy between the two products. Demonstrating that the FOB's mechanism of action, and the specificity of target interaction in applicable cases, is the same as the innovator product will be key to demonstrating that an FOB is sufficiently similar to an innovator so as to permit use, to some extent, of the safety and efficacy already demonstrated with the innovator product.

In some cases the mechanism of action is not well defined or understood for the innovator product; however, the product will still have been approved based on the safety and efficacy data reviewed by FDA for the approved indication. In those cases it would not be reasonable to require that the FOB applicant determine the mechanism of action and then ensure that both products share the same mechanism of action. However, sufficient data to support that the FOB is sufficiently similar in the proposed indication to the innovator product in regards to structure, function and clinical results in humans, would still be necessary and critical.

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?*

Almost all biological products consist of more than one biochemical entity; therefore it is very difficult to quantify the degree of variability in chemical structure. Compared to many small molecule drug products, proteins are usually substantially larger, more complex molecules that may be mixtures of distinct entities. Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variations in the manufacturing process.

Modifications to the manufacturing process have the opportunity to introduce additional changes, including changes to the product or process impurity profile, which may affect the safety or efficacy of the product. The same manufacturer may be able to demonstrate that a product made after a manufacturing change is comparable to a product made before implementation of the change. This may be demonstrated through different types of analytical and functional testing, including assessment of historical batch and stability data and analysis of in-process data, and might not require additional human clinical studies. FDA may determine that the two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency.

Typically, demonstrating the similarity of an FOB to an innovator product will be more complex, and thus require more new data than required to effect a manufacturing change. It may also require additional testing than would typically be required for assessing the similarity of products made by the approved product's manufacturer before and after manufacturing changes.

In regard to the naming and interchangeability of FOBs, refer to the response to Question 5 of the Science/Safety section and to the responses to Questions 1-2 of the Interchangeability section for our recommendations.

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?*

We believe some level of human clinical trials should be mandated for all FOBs.

However, FDA should be given discretion regarding the scope of such trials, provided that the Agency addresses these issues in product-class specific guidance. This will ensure that the American public is exposed only to FOBs that are demonstrated (1) to be safe and effective, and (2) not to result in adverse immune responses.

The standard for approval of a biologic under the Public Health Service Act ("PHSA") is "safety, purity and potency." The standard for approval of FOBs under the FFDCA is "safety and efficacy." Under either standard, the assessment of the FOB will be technically complex and will require the expertise of the scientists within the sponsor company and the reviewers and technical staff within FDA to determine what evidence must be generated to support approval of the product. However, with the uncertainties associated with complex biological molecules, we believe that an FOB should not be approved in the absence of human clinical data.

If some level of human studies is not mandated for FOBs, then critics of an abbreviated FOB review pathway are likely to question publicly the safety and efficacy of FOBs. This may cause some physicians to refuse to consider FOBs for their patients. Furthermore, this could result in patients instructing their physicians not to allow substitution of their brand biologic with an FOB. It may be practically necessary, even in the absence of mandatory guidance, for sponsors of FOBs under a newly-approved paradigm to perform human clinical studies to confirm that the FOB is sufficiently similar to the brand biologic and establish a foundation for understanding the variations between FOBs and brand biologics.

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?*

FDA and FDA officials have publicly discussed the studies it has required and the extent to which it has relied on existing data in evaluating protein products under the FFDCA. For more information on this question, please refer to the following sources:

- Letter from S. Galson, Director of the Center for Drug Evaluation and Research at FDA to K. Sanzo, S. Lawton and S. Juelsgaard, re: Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 (May 30, 2006).

- Statement of J. Woodcock, Deputy Commissioner and CMO, FDA before the House Committee on Oversight and Government Reform, "Follow-on Protein Products" (March 26, 2007).

- J. Woodcock, et al., *The FDA's assessment of follow-on protein products: a historical perspective*, Nat. Rev's Drug Discovery at 1 (April 13, 2007) advance online publication.

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?*

We were not involved with this review process and we have no direct knowledge of this approval.

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?*

In order to maintain consistency and to build appropriate review expertise, we recommend the creation of a single FOB approval process for all biologics, including those approved under the FFDCA instead of the PHSA. Such an approach will minimize the uncertainty and potential conflicting review outcomes that could otherwise arise if future FOB applications could be filed under different statutory sections.

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?*

At this time, we do not have an approved biologic on the market. In general, however, although the current statute gives FDA discretion to decide when a change in an approved biologic merits clinical trial investigation in humans, we note that discretion is limited. While we support the creation of dynamic and flexible statutory and regulatory mechanisms, our main focus is on ensuring that safe, effective, and continually improved biologics reach the public. To achieve this goal, it is vital that an appropriate standard is developed and consistently applied. We encourage the Committee to consider the effect that any proposal would have on maintaining and applying a consistent review standard across highly variable products and applications.

3. *What FDA office should review FOBs?*

As FDA has publicly acknowledged, "there is general recognition that the idea of sameness, as that term is used in the generic drug approval process under the [FFDCA] and applied to small molecules, will not usually be appropriate for more structurally

complex molecules of the types generally licensed as biological products under the Public Health Service Act."[1] Furthermore, due to the size and complexity of most biologics, FDA reviewers face greater analytical challenges in trying to characterize and predict the clinical effects of an FOB in humans than they would assessing the effects of a generic small molecule drug. Given the complexity of these analyses and the need to maintain consistency across the review of all biologics, we recommend that a group within CDER be charged with reviewing FOBs. This authority should not be given to the Office of Generic Drugs, as the work done in that office is significantly and critically different from the work that will be necessary to review FOB applications.

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?*

The standard for assuring sufficient similarity between the FOB and the reference product should be the "highly similar" standard. The alternative proposed standard of "as similar as scientifically possible" has no anchor in science, because the methods and techniques used to test and characterize biologic compounds are constantly changing.

FDA can begin to assess a biologic under the "highly similar" standard by utilizing the approach used by innovators who make changes to an approved biologic. Innovators use comparability studies to predict the clinical performance in humans of biologics produced after manufacturing changes. Comparability testing programs may include a combination of analytical testing, biological assays (*in vitro* or *in vivo*), assessment of pharmacokinetics and/or pharmacodynamics and toxicity in animals, and human clinical testing (clinical pharmacology, safety, efficacy, immunogenicity), with the usual progression of complexity from analytical to animal studies to human pharmacokinetics and/or pharmacodynamics to human clinical safety and efficacy studies.

When performing comparability studies, FDA requests that manufacturers provide extensive chemical, physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. Additional testing usually includes in-process assays at the manufacturing steps which are most likely affected by the manufacturing changes. To the extent that analytical techniques for characterizing biologic products continue to improve, with increased sensitivity and ability to detect structural aspects of biologics, the ability to analytically predict comparability will continue to improve.

However, innovators use their knowledge of the product's manufacturing process in determining the design of an appropriate comparability assessment program. The use of an analogous comparability approach by an FOB applicant is hindered because the FOB applicant has minimal information regarding the manufacturing process of the reference product. For this reason, an FOB applicant will need to go beyond the physico-chemical

[1] Statement of J. Woodcock, Deputy Commissioner and CMO, FDA before the House Committee on Oversight and Government Reform, "Follow-on Protein Products" (March 26, 2007).)

analytical techniques that might be relied on by an innovator making a manufacturing change and include a human clinical component to the comparability assessment.

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?*

As noted above, we believe the success of an FOB approval pathway depends upon the creation of a mechanism that adequately safeguards patient safety, ensures the effectiveness of all biologics on the market, and preserves the incentive to develop and produce new and better therapies. Due to the variety and complex nature of biologics, we would encourage the Committee to mandate by statute that FDA produces product-class specific guidances that address the data requirements and the anticipated human clinical investigations associated with evaluating a particular class of biologic products. Such guidances should be subject to public notice and comment to promote a candid and transparent discussion of the information needed to demonstrate an FOB in that product class is safe and effective. These guidances will then serve to establish the standard appropriate for the evaluation of all FOBs within a particular class.

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?*

Given the highly complex analyses required to evaluate an FOB application, we favor the creation of FOB user fees. It would not be appropriate or acceptable to divert user fees for drugs or biologics to review of FOB applications, since doing so would compel innovative manufacturers to subsidize the review of competitor products. We recommend that a ratio of user fees to base appropriations similar to the ratio applied to the review of new drugs and/or biologics also be used for the review of FOBs.

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?*

An assessment of interchangeability of an FOB goes beyond the threshold assessment of determining whether the FOB is sufficiently similar to the innovator product. Dosing similar biologic products back-to-back, or "switching" between doses of the FOB and innovator product, brings additional concerns. Interchangeable FOBs should be expected to produce the same clinical results in humans as the reference product and present no additional risk in terms of safety or change in efficacy if a patient switches between

products. There are many scientific studies that can be done to assess similarity as the first step toward assessing interchangeability.

While not every conformational detail of a biologic may be determinable, much is open to detection by a variety of analytical techniques. These methods continue to evolve and improve. Biological models, both *in vitro* and *in vivo*, provide valuable information regarding mechanism of action. Pharmacokinetic and pharmacodynamic studies determine how the body absorbs, distributes, metabolizes and excretes a biologic. They also assess the effect of the biologic on animal and human physiology. Toxicology studies will determine the predicted safety issues at relevant clinical doses for humans and will establish maximum tolerated doses for comparison with the reference product. Human clinical studies (pharmacology, safety, and efficacy) can provide actual data on how the biologic will affect the patient.

However, due to the complexity of biologic compounds, to ensure the safety of the patient, a human clinical switching study should be required to demonstrate interchangeability. A human clinical switching study requires that the FOB and innovator product be given to study participants on a "switching" or back-and-forth dosing schedule. The data from the study will ensure that there are no unanticipated safety issues, that the pharmacokinetic/pharmacodynamic profile of the patient remains unchanged, and that no immunogenic response is induced. This type of study should be required because of the difficulty in analytically determining the method of action of a biologic compound, the potential differences in safety and efficacy that may come out of apparently minor differences in receptor binding, and the overarching concern and risk of inducing an immunogenic response. Until science can reliably predict the complex biological interactions associated with biologic products, human clinical switching studies should be a prerequisite to a determination of interchangeability for FOBs.

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

In addition to the requirement to determine that the FOB is "highly similar" to the reference product, the standard expressed by Dr. Janet Woodcock of the FDA in her statement before Congress on May 2, 2007, sets a reasonably prudent standard for a determination of interchangeability. "To establish that two protein products would be substitutable, the sponsor of an FOB would need to demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity." Dr. Woodcock's statement expresses a recognized safety concern. An immunogenic response may manifest itself as a dangerous, life-threatening condition, or may result in a lack of efficacy, which may be equally dangerous for a patient in need of effective treatment for a serious disease.

As we have noted, we support granting FDA discretion to determine which studies and data will be necessary and sufficient to permit approval of an FOB, but we believe such discretion should be exercised only pursuant to the development and publication of product-class specific guidances mandated by statute. It is our belief that, since there is a

fundamental difference between the approval of a non-interchangeable FOB and an interchangeable FOB, FDA should also address the additional requirements for approval as an interchangeable FOB as part of product-class specific guidance.

At this time, we believe, the data needed to determine interchangeability, *i.e.*, similar clinical results in humans with no increased risk of safety, would likely include the data required to determine that the FOB is sufficiently similar to the reference product to support approval with the additional requirement of human clinical switching studies. These techniques include analytical testing, biological assays (*in vitro* or *in vivo*), assessment of pharmacokinetics and/or pharmacodynamics and toxicity in animals, and human clinical testing (clinical pharmacology, safety, or efficacy). Clinical switching studies in humans will provide confirmation that switching back-and-forth between an FOB and a reference biologic will not induce an immunogenic response.

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.*

The unique risk to patients from interchangeability of biologics is the potential for an immunogenic response. This is a risk that is not faced by patients who switch back-and-forth between small molecule generic drugs and their brand name equivalents. An immunogenic response may manifest itself as a dangerous, life-threatening condition, or may result in a lack of efficacy, which may be equally dangerous for a patient in need of effective treatment for a serious disease.

Given our current level of knowledge, however, a finding of interchangeability will be technically difficult, if not impossible. Although we can ascertain the primary structure of a protein - the exact sequence of amino acids of which it consists - understanding and proving that such a sequence will have the same clinical effect in humans as another product and with no adverse effect to a patient when used interchangeably is quite difficult. As FDA has noted: "the amino acid sequence is the most rudimentary characteristics of a protein. Conclusive analysis of other aspects of a protein's amino acid chain into highly organized structures requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself."[2] In light of these scientific challenges, product-class specific guidance will clearly be necessary, and in some, if not all, cases, should prohibit a finding of interchangeability until more appropriate technologies are available. We support proposals to develop such guidance based on validated scientific findings and drafted through transparent processes, including public notice and comment.

The standards regarding interchangeability of biologics should be established such that risks to patients are minimized.

---

[2] Statement of J. Woodcock, Deputy Commissioner and CMO, FDA before the House Committee on Oversight and Government Reform, "Follow-on Protein Products" (March 26, 2007).

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?*

We recommend that FDA not accept an application for an FOB in the absence of product-class specific guidance, which has been subject to public notice and comment. Until FDA and the public, through notice and comment processes, have been able to consider and discuss the types and amount of data and information required for approval as an interchangeable FOB, it is premature to submit such an application. First, without such guidance it is unlikely the applicant would know which information would be needed to evaluate the application until FDA establishes what that information is. Secondly, in an era of tight agency resources, it is inefficient to review an application before the Agency has determined what information it needs to adequately assess the safety and effectiveness of the product.

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?*

The unique risk to patients from interchangeability of biologics is the potential for an immunogenic response. This is a risk that is not typically faced by patients who switch back-and-forth between small molecule generic drugs and their brand name equivalents. An immunogenic response may manifest itself as a dangerous, life-threatening condition, or may result in a lack of efficacy, which may be equally dangerous for a patient in need of effective treatment for a serious disease.

The standards regarding interchangeability of biologics should be established such that risks to patients are minimized. If this standard is appropriately applied, the decision about whether to substitute an FOB for a reference product can safely be made only by the physician.

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

We do not believe we are qualified to provide a detailed answer to this question. Our chief concern is to ensure that all biologics marketed in the United States, whether innovative or biosimilar, are safe and effective, and do not in any way diminish the safety and efficacy of an entire product class. As discussed above, due to the unique challenges posed by assessing the immunogenicity of an FOB, an inappropriate finding of interchangeability will clearly harm innovation, because it could result in adverse safety and efficacy effects across a class of products. It is crucial that science and patient safety, not economics, be the driving force behind any findings of interchangeability, because if it is not, public confidence in biologics as a whole will be undermined.

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?*

   We are unaware of any readily available current statistics measuring effective patent term using the parameters of this question. Therefore, we are not qualified to answer it for this inquiry.

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?*

   The Hatch-Waxman Act, which allows for the restoration of innovator patents up to a 14 year term and provides five years of data exclusivity for small molecule drugs, does not provide the proper model needed for biologic manufacturers. As discussed elsewhere in our response, the regulatory approval process for biologics is fundamentally different from the regulatory approval process for small molecule drugs. Not only are the time horizons longer, but there are additional complexities associated with biologics that begin with discovery and run through development, approval, and on-going manufacturing processes. In view of these extensive efforts, it is essential that a sufficient period of data exclusivity be granted to innovator biologic manufacturers to provide the appropriate incentive to promote advances in new medicines. Without adequate protections, we believe the incentive to turn new biotechnology discoveries into innovative therapies will greatly diminish.

   We do not believe that the current period of data exclusivity under the Hatch-Waxman Act is sufficient to ensure the essential growth of a viable biopharmacuetical sector over the long term in the U.S. Because FOBs will not be identical to the innovative products they are attempting to copy, on occasion, an FOB may be sufficiently different from the innovative product so as not to infringe the innovator's patent, especially given the vagaries of patent law. In such cases, the FOB would be able to be approved solely on the basis of the innovator's data and the innovator's patent protection would provide no exclusivity. Therefore, given the significant investments of time and capital associated with generating sufficient data to demonstrate safety and effectiveness, if an innovator does not receive an adequate period of data exclusivity, innovation will suffer and new treatments will go undeveloped.

   The lesson learned from the Hatch-Waxman Act is that the patents covering a molecule and data exclusivity provided by FDA are independently important, and both periods of protection must be sufficiently strong to encourage innovation. The Hatch-Waxman Act has clearly met its goal of fostering generic competition for innovator drugs, but it is less clear whether more new and improved products are reaching American patients. We support legislation that both promotes a more competitive biologics marketplace and does not prevent patients from realizing the benefits of advances in science and technology.

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?*

According to Article I, Section 8 of the Constitution, patents are intended to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." In the context of science and medicine, the patent system helps ensure that technological discoveries are transformed into important treatments for patients who need them. Patents clearly are an important and vital part of the incentive mechanism that fosters the discovery and development of new medicines.

However, due to the differences between small molecule drugs and biologics, the scope of protection afforded by a patent is narrower for a biologic than a traditional drug. With respect to small molecule drugs, the key patent protection is on the active pharmaceutical ingredient, which, if patented, cannot be copied by a competitor during the term of protection. A patent on an innovator biologic, however, may not be infringed by a "highly similar" biologic. Thus, although patents for biologics provide critical incentives, particularly during the period of initial discovery and development, the protection that they offer should not be compared to that of the patents on traditional small molecule drugs.

As our goal is to ensure that new therapies reach the patients who need them, we would support legislation that maintains incentives for innovation and rewards sponsors who demonstrate, through a fair and efficient process, that their products are safe and effective. For this reason, we believe it is essential that any abbreviated FOB approval pathway incorporate both patent protections and appropriate periods of data exclusivity, for both innovators and those FOB sponsors who submit extensive data packages of their own.

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?*

Identifying relevant patents and ensuring timely resolution of legal disputes before an FOB receives approval should be an important aspect of any FOB legislation. 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. 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. This is particularly important to smaller commercializing biotech companies who often do not have the resources to defend themselves from patent infringement by larger, multinational generic firms expected to participate in the FOB market.

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?*

Third party patents play an important role with respect to biological products, particularly in the areas of manufacturing and platform technology. 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 an 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. 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 efficient for the legislation to provide for a direct exchange of patent information between patent owners and FOB applicants.

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?*

First, it is important to note that data exclusivity is not the same thing as market

exclusivity. Data exclusivity refers to the period of time during which innovator manufacturers have exclusive use of the proprietary data which they generated to support a finding of safety and efficacy of a product by FDA. Market exclusivity provides a product exclusive access to a market and currently exists only in the context of the Orphan Drug Act. Outside of the Orphan Drug context, multiple products can compete in the same market space under current law, assuming they each submit a complete BLA to FDA with all necessary data, and assuming FDA finds each product to be safe and efficacious in its own right. See, for example, the current markets for insulin, human growth hormone and beta interferon.

FOB manufacturers will, by definition, gain approval for their product by relying, at least in part, on FDA's prior finding of safety and efficacy of an innovator product, which was based on that innovator's proprietary data. Given the vagaries of patent protection for pharmaceuticals and biologics, we believe innovative manufacturers require 14 years of data exclusivity to provide sufficient incentives for continued innovation. We further believe that patent disputes can be resolved within this 14 year timeframe, rather than subsequent to it.

To preserve the incentive to expend the costs and time to develop innovative biologics, it is essential to ensure that innovators can rely on both their patent protections and a period of data exclusivity. Patent protections allow innovators, particularly small biotechnology based companies, to bridge the so-called "valley of death" during the intensive research and development (R&D) phases associated with bringing a safe and effective biologic to market by offering them the potential to recoup their significant investments in R&D. Data exclusivity protection serves a different purpose. It provides a set period of time during which the R&D investments that an innovator makes cannot be used to directly subsidize the efforts of a potential competitor. Given the capital intensive nature of innovative biologics R&D, if an innovator were to lose such data exclusivity prematurely, it would have a chilling effect on investments in the development of new technology and products.

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?*

Please refer to studies conducted by Henry Grabowski at Duke University for such an assessment.

We support BIO's proposal of 14 years of non-patent data exclusivity, in addition to the patent protections attached to any given product. As BIO has noted, "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."

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

Modifications to an existing product, which improve its safety, expand or enhance its effectiveness, or render the product more accessible or patient-friendly, should be

rewarded. We support grants of market exclusivity for modifications, such as those described here, which result in improvements that make the lives of patients better.

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

From the filing of an IND to the NDA approval, it costs over a billion dollars to develop a drug over the course of a 10 to 15 year period. The data exclusivity for that approved drug provides the innovator at least the assurance that for a fixed period of time they will not experience generic competition for their drug. For a few products, such a limited time of data exclusivity will provide sufficient incentive for an innovator to develop the drug. Generally, patent protection is considered a prerequisite for an innovator to spend the vast sums of money necessary to obtain a drug approval. Unlike data exclusivity which only prevents a generic manufacturer from using the innovator's work to get a copy of the drug on the market, patent protection can be used to prevent other innovator companies from developing similar drugs for an indication. Both forms of intellectual property are important to innovator companies. Given the shortness of exclusivity provided by Hatch-Waxman (5 years of data exclusivity for new chemical entities), patent protection is also important for rewarding innovation. This is all the more important for biologic products, which are incredibly complex and expensive to make as compared to small molecule pharmaceuticals.

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

Because biologics are more complex and expensive to research, develop and gain market approval, they should receive a much longer period of data exclusivity than drugs. In addition, in the case of small molecule drugs, generic versions are approved on the basis of "sameness" which makes a finding of patent infringement easier to determine. Thus, patents provide a greater degree of exclusivity for small molecule drugs in the context of generic competition.

With respect to FOBs, however, the standard is "similarity." In such cases, a product might be similar enough to allow FDA to rely on the previously submitted innovator data to find the FOB to be safe and efficacious, but the product might have been designed in such a way that it falls outside the scope of the innovator's patents relating to the products. Thus, both patent protection and data exclusivity are critical intellectual property protections for biologics. We believe a data exclusivity period for biologics of 14 years, with a patent dispute resolution system that operates during such time rather than after it ends, provides the right balance of data exclusivity to meet the need for continued investment in innovation and the need to bring to market safe and effective FOBs.

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

We believe that data exclusivity and patent protections should be established as the principal forms of intellectual property protection for biologics. As noted above,

innovator companies must spend billions of dollars to obtain FDA approval for their drug applications, often using up significant portions of patent life to do so. When the Hatch-Waxman Act was passed, the generic industry was in its infancy, but now generic companies are large, multinational corporations. Over the past 24 years, several of the companies in the generic industry (*e.g.*, Teva) have grown to a size where their market capitalizations approach or surpass the market capitalizations of some "Big Pharma" companies as well as surpassing the market capitalizations of all but three biotech companies (Amgen, Gilead, and Genentech). In contrast, there remain a significant number of smaller biotech companies, whose continued ability to research and develop new and innovative products is dependent on the revenues that are generated during the period of data exclusivity and patent protection for their product or products. These revenues are the fuel that drives the pipeline of these smaller companies, allowing them to bring forward important new therapies to patients.

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?*

Some of the most important innovations and advances in patient care have come from the labs of small biotech companies. If an FOB pathway were created without any data protection for innovator products, beyond current patent protections, innovation would suffer. Development of biological products is a long-term, expensive, and risky undertaking. Products can take 10 to 15 years to develop, with an investment well above $1 billion dollars per product, and significant risk of failure. Innovator companies require a period of data exclusivity to recover the significant investment in a product and secure sufficient returns to conduct the additional research and development that drives innovation. Furthermore, without these sorts of incentives small biologic companies and the capital markets they rely upon will not be able to bring new innovations to patients. Continued research and innovation requires a period of data exclusivity, not just patent protection, due to the importance of both of these forms of intellectual property protection to the biotechnology industry.

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.*

We are not qualified to answer 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?*

We are not qualified to answer this question. However, we believe there is value in smaller, emerging companies who invest billions of dollars to bring products to market. Companies such as Millennium often burn capital for years before returning a profit to investors who believe in smaller companies. Those first biologic products for an emerging company provide the fuel to fund the human clinical programs and development of subsequent therapeutics.

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

The U.S. is the world-leader in the field of biotechnology. The key factor behind this success is that the investors in this field (*e.g.*, scientists, universities, biotechnology companies, venture capitalists and other suppliers of human and real capital) believe that the fruits of their investments will not be misappropriated by competitors. An FOB pathway that does not afford strong intellectual property protection (*i.e.*, 14 years of data exclusivity) for new products will make the field of biotechnology less attractive for such investors, thus harming U.S. economic competitiveness. In addition, the chilling effect of capital flight to other sectors will force smaller biotech companies to reduce their pipeline investments and place at risk innovations important to American patients.

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?*

Because of the length of time and the amount of investment required to bring a biologic product to market, strong and predictable patent protections are vital. Without such protections, it will be hard to attract and sustain investment in this field. Discovering, developing and bringing novel biologic products to market is financially risky, requiring a number of research avenues be explored and abandoned in order to find those that lead to safe and effective new products. Patents provide critical incentives for investing in biotech inventions, because of the potential to recoup that investment at a future point in time. If such protections were weakened, without providing an alternative means of recouping invested funds, investors and top scientific talent will turn their efforts towards areas where the potential for growth and earnings is not diminished. If this were to occur, it would undoubtedly have a chilling effect on breakthroughs and innovation in the biotechnology sector, and will also likely result in many promising technologies being developed at a slower pace, if at all.

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?*

The development of a novel biologic product involves intensive investments of human and capital resources. If incentives to drive innovation are lacking or inadequate, promising scientists and investors are likely to focus their resources and efforts on other areas. This would have an immediate and drastic impact on biotechnology companies and university research programs. If adequate funding is not available in either the private or university setting, cutting edge research programs will wither as top talents in science pursue other disciplines.

We recognize the need to balance incentives for innovation against increasing competition in the biologics marketplace. If, however, this balance is not struck appropriately, then neither innovation nor competition will exist, because if new products are not produced, there will be no products to reference to increase competition. We support the development of an abbreviated review pathway that ties powerful incentives, such as incremental increases in exclusivities, to real innovation. In this way, innovators can demonstrate their viability to scientists and investors, which will drive innovation, leading to more therapies for patients, and ultimately, to more products to reference for FOB manufacturers.

European Model (abbreviated approval pathway)

While we appreciate the Committee providing us the opportunity to comment on these issues, we have no relevant experience to share with the Committee with respect to the section below, because we do not market any products in the EU.

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?*