INSMED
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April 29, 2008

Frank Pallone, Jr.
Chairman
Subcommittee on Health

Nathan Deal
Ranking Member
Subcommittee on Health

Dear Members of the Subcommittee on Health,

On behalf of Insmed Incorporated, I would like to thank you for inviting Insmed to participate as a stakeholder in the discussion on creating a pathway to allow the Food and Drug Administration (FDA) to approve follow-on biologic products. We share the Members desire to provide American consumers with safe and effective biologic medicines that will lower the cost and expand the access to these life saving medicines.

Attached hereto are our responses to the questions raised in the April 3, 2008 letter from the Committee on Energy and Commerce. I hope that these answers help the Members appreciate Insmed's perspectives as you work towards legislation.

I look forward to helping the Members in any way that is possible. If you need any clarification or would like to discuss our responses, please contact me at (804) 565-3010 or by email at gallan@insmed.com.

Sincerely,

Geoffrey Allan, Ph.D.
President and Chief Executive Officer
Insmed Incorporated

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 a biological response against a foreign substance, such as antibodies directed against a drug product (termed "anti-product antibodies").

Immunogenicity is a concern for biologics and non-biologics alike. All biological products are potentially immunogenic. However, immunogenicity is not unique to biologics. For example, there are well known strong immune responses to common non-biological drugs such as penicillin. More recently, impurities found in heparin products are suspected to have led to severe allergic reactions resulting in a significant increase in reported adverse events including possible fatal outcomes. Although biological products are inherently immunogenic, in most cases immunogenicity has little or no clinical effect. In fact, some biologics are well-recognized to be very weakly immunogenic, such as granulocyte colony stimulating factor (G-CSF). When anti-drug antibodies are reported for biologics, clinicians usually continue treatment of patients as antibodies frequently disappear or lessen over the course of treatment. In fact, when protein products are approved and used in the patient population for which the product is indicated, antibody measurements are not usually taken and it is not known if antibodies develop unless clinical symptoms appear that can be directly correlated to anti-product antibody formation. In effect, the medical field does not view antibodies with concern unless there is a clinical consequence. One rare clinical consequence is when antibodies develop that neutralize the effect of the biologic. This can result in decreasing the efficacy of the therapy and in some rare cases can result in cross reactivity with the patient's own protein. Thus, the clinical consequences of antibodies, not the development of antibodies *per se*, are of significance.

Immunogenicity is certainly something to be aware of, but its importance should not be viewed outside of the overall safety profile of the biologic product. The risks associated with the current targets for FOB development – growth hormone, insulin, the alpha and beta interferons, granulocyte-colony stimulating factor (G-CSF), and erythropoietin (EPO) – are very well understood and generally represent a low safety risk to patients. In addition, some of the triggers of immunogenicity are known; immunogenicity is not entirely unpredictable. For example, one trigger is molecular aggregates. As a consequence, considerable attention is paid to avoiding aggregates through suitable formulation and monitoring for aggregates during process development and during stability studies.

The only approved product in which neutralizing antibodies have presented a significant safety risk for patients who develop antibodies is EPO. In Europe there was an increase in the number of patients with antibodies against *epoetin alfa*, in which antibodies inhibited the patient's own EPO and prevented the body from producing its own red blood cells (called pure red cell aplasia or PRCA). According to published reports released by the manufacturer of this product, this was a result of manufacturing changes

(a change in the stabilizer and the vial stopper). This risk has been largely mitigated and currently is a very rare event.

Do immunogenicity risks vary depending on the type of biologic? Yes. In some cases immunogenicity is rare and there is no documented evidence of untoward effects of the antibodies – such as for products like NEUPOGEN (*filgrastim*). In other cases, antibodies are more common, such as for the beta interferons (such as BETASERON). In these cases, the antibodies may be neutralizing in biological assays, yet it is not clear if the antibodies attenuate or neutralize the therapy. The worst case scenario is when neutralizing antibodies may develop that cross react with a natural protein and place the patient at new risk due to their occurrence, such as in the PRCA case with *epoetin alfa* (even though it is an extremely rare event - ~1:10,000).

A risk–based approach is taken to evaluate and mitigate the risks of immunogenicity prior to the initiation of every clinical trial for a biologic, whether the product is a new chemical entity (NCE) or a biosimilar. This approach includes the conduct of a risk analysis and risk mitigation strategies designed into the clinical protocol and the clinical setting. Many factors can lead to immunogenic reactions including the size and structural complexity of the molecule, impurities, target disease, patient population, route of administration, dose and frequency of administration. The higher the potential for immunogenicity to adversely effect a patient's health, the more diligently immunogenicity is examined. This approach is required by the FDA as part of the clinical development program for every biological product.

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 type of studies, are needed on a case-by-case basis?

For FOBs, the FDA should be given discretion to determine what types of studies are needed on a case-by-case basis using the risk-based approach described above.

As stated in question 1, the current FOB targets pose little risk for patients and so the FDA should have its discretion on implementing requirements for FOB applicants of these products. Furthermore, the FDA should be given discretionary authority because the risk analysis is unique for each product and no statutory mandate (one size fits all) could possibly work. Moreover, as science evolves and new products are introduced, the FDA should not be restricted by statute.

Moreover, there are practical limits to what can be expected pre-approval for an FOB. In the case of *epoetin alfa*, the incidence of PRCA was ~1:10,000. If the FDA were to mandate robust immunogenicity testing pre-approval, the minimum clinical trial size to ensure that you could even detect an antibody response of this type would be approximately 50,000 subjects. The trial size to compare antibody responses of two products would be substantially larger. If such testing were mandated, no FOB products

will be developed to provide competition in the US for EPOGEN because the cost for development will simply be too high. In addition, as immunogenicity is an issue for innovative biologics, this requirement would also impede the discovery and development of new biological products. In such cases, the proper method for monitoring rare adverse events is through post-approval safety surveillance.

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 mandatory?

The FDA should be given discretion to determine what types of studies are needed on a case-by-case basis for manufacturing changes. This is the current operating mode within the FDA and in the International Conference on Harmonization (ICH) guidance documents.

After the discovery of the PRCA risks associated with EPREX (*epoetin alfa)*, the FDA did not require the US approved EPOGEN or PROCRIT product removed from the market and new clinical trial evaluation to evaluate immunogenicity risk. Instead, the manufacturers monitored the safety of the drug through careful post-marketing surveillance. This proved an effective mechanism to resolve the manufacturing problems while still providing patients access to therapy. Importantly, it was the implementation of more rigorous analytical testing that helped resolve this manufacturing issue rather than new clinical trials.

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

For products in which the clinical mechanism of action is well defined and understood, the FOB applicant should receive labeling claims for all indications upon demonstration of similarity, safety, and effectiveness in one 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 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?

The FDA should apply the same authorities to FOBs as those granted under FDAAA for reference products. It is reasonable that the FDA request that the applicant monitor typical safety evaluations of an FOB as would be applied to the reference product since

their safety profiles will be similar to each other. As such, FOB applicants should not be required to conduct any unique or different types of studies that have been requested/required for reference products.

Given the possibility of drug-induced antibodies, however, it may be appropriate for the FDA to require a post-approval study to monitor the immunogenicity of some FOB products as part of their overall post-approval safety evaluation on a case-by-case basis.

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 name, including any affect on patient safety? What alternatives are available?

Non-interchangeable FOBs should have the same non-proprietary name as the reference product because they are the same chemical entity. From a practical perspective, a statutory requirement to require different names for essentially the same drug would represent a departure from the current standard within the FDA and the current medical practice. For example, there are several growth hormone and insulin products on the market. In both cases, the INN is the same for all similar products. To have different names give rise to the risk that a patient could receive a prescription for two similar products and as such increase the risk of overdose with a class of drugs.

The approvals of growth hormones provide an example of where several non-interchangeable products share a common proprietary name. Similarly, a non-interchangeable FOB product will have a distinct brand name, but the same non-proprietary name. If a physician chooses to prescribe the reference product, then he/she is free to write the prescription for the brand name product. Conversely, there is considerably higher risk of confusion for the physician if both the brand name and the non-proprietary name of the FOB are different from the reference product.

The standard for an interchangeable FOB should be that the product can be substituted (patient switching) with the reference product without adverse effects to the patient. Should an FOB product be awarded interchangeable status, then it should receive the equivalent of an "AB" rating and this will signal the pharmacist that a substitution could occur.

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 for 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, it is important that an innovator and an FOB have the same mechanism of action. An FOB and a reference product will have the same mechanism of action because they are the same chemical entity.

Each of the current targets for FOB development (growth hormone, insulin, the alpha and beta interferons, G-CSF, and EPO) has a very well-defined mechanism of action. Each product binds to a specific receptor to elicit a biological effect. As part of product characterization, the FOB applicant should assess multiple parameters of biological function including mechanism of action by evaluating parameters such as receptor binding, *in-vitro* bioassays, animal pharmacology, and pharmacokinetics. For products where the correlation between the mechanism of action and its role in disease management is not known, a comparative clinical study could be used to establish a similar mechanism of action through clinical outcomes.

An FOB applicant should not be required to demonstrate a scientific principle that was not required by the innovator. Some scientific questions are unknown (and may be unknowable) but do not impact the basic evaluation of clinical safety and efficacy. For example, the correlation between beta interferon's mechanism of action and how it impacts disease management in multiple sclerosis is not well understood, but this has not impacted the FDA's ability to establish its clinical safety and efficacy.

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?

There is typically very little variation in the base chemical structure of a biologic. Variability may be seen in minor contaminants or minor product variants. The other area of potential variability is in the glycosylation pattern for products produced in systems capable of adding sugar moieties to the protein. Demonstration of batch-to-batch consistency and comparability of the product produced after a manufacturing change are required for approval. Insmed does not have access to the reference product's manufacturing data and so it cannot know all of the batch-to-batch variability that exists over the history of the reference product. Similarly, Insmed cannot know the variability that is introduced during manufacturing changes for the reference product. However, Insmed routinely tests comparator products and uses this information to guide it in establishing appropriate specifications for its FOB products. Insmed believes that FOB products should be made to the same standard of identity, purity, safety, and potency as the reference products.

It is important to understand that the first FOB products are "well-characterized biologicals" and as such it is presumed that their chemical identity, purity, impurity, potency, and quantity can be determined and controlled. When industry and FDA were discussing regulatory changes in the late 1990s regarding these products, prominent scientist from industry acknowledged this fact. For example, Dr. Stuart E. Builder from

Genentech indicated in a paper discussing product comparability that "...the nature of the product can now be separated from the process that made it. I think that taken together we have established a way in which to use careful analysis to demonstrate more effectively and more efficiently that **two processes, facilities, or pieces of equipment can produce a substitutable product**" (Lubiniecki and Murano (eds): Characterization of Biotechnology Pharmaceutical Products. Dev Biol Stand. (1998) vol 96 pp 83-90).

Each FOB will be approved with its own specifications that are established by evaluation of the characteristics of the reference product, shelf life stability, and by the FOB applicant's proprietary process capabilities. The FOB applicant is responsible under the current regulations to report the status of batch-to-batch variability and any changes to specifications on prior approval, timed basis, or annually.

If the FDA determines that an FOB product is interchangeable, then the Agency will have been convinced by evidence provided by the applicant that the FOB and the reference product can be safely substituted. If there were evidence that either product (the original innovator or the FOB) failed to meet the obligations of their approval, then the FDA has the authority to suspend or withdraw that approval *of either product*.

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 marketing acceptance? Why or why not?

The FDA should be given discretion on a case-by-case basis to establish if clinical trials are necessary to approve an FOB product.

When the FDA approves a drug, the American public trusts its judgment. This can be seen though the public's acceptance of generic drugs after the implementation of Hatch/Waxman. There is no reason to believe that market acceptability of FOBs would be different.

The market acceptance of FOBs could be impacted by factors such as the complexity of the drug, the physician's knowledge and comfort with the drug's mechanism of action, the use of the drug in disease management, and the product presentation and ease of use. For example, drugs such as insulin, growth hormone, and G-CSF are relatively simple structural molecules with well defined mechanisms of action and long histories in their use in disease management. In such cases a physician could have confidence in an FDA approved FOB that wasn't supported by human clinical trials. Conversely, beta interferon, which is a compound where the drug's mechanism in action is not well correlated to its use in disease management, may require human clinical trial data to demonstrate acceptance by a treating physician.

It is worth noting that the FDA and the public have had vast experience with some of these drugs, which have been approved for use since the early 1990's. By the time FOB

products are available for market, some of these products will have been on the market for more than 20 years.

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

There are limited examples of biologic drugs approved under 505 of the FD&C Act since most biologic products were approved under the Public Health and Safety (PHS) Act. To our knowledge no protein product has been approved without clinical trials.

Humatrope® was the first recombinant human Growth Hormone (hGH) product approved in 1987. Prior to this approval, FDA made the decision that abbreviated safety and efficacy clinical trials could be performed in 50-100 patients for 6 months for all hGH products. The rationale for this decision was that hGH is a simple protein that can be adequately characterized; identity, potency, and purity of hGH products are well established; and there was a product already on the market to which identity, safety, and efficacy could be compared (pituitary-derived hGH). All hGH products were approved through this abbreviated clinical program. For Humatrope, FDA made the determination of safety and efficacy based on literature and clinical trial data submitted for the natural protein product and other recombinant hGH products. It is likely that these data supplemented the data obtained through the abbreviated clinical trial program.

In the 21 years since Humatrope approval, 6 additional hGH products have been approved in the US. These products have been marketed simultaneously throughout this time period and have a consistent record of safety.

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?

Regarding the safety of OMNITROPE since it was introduced to the US market, Insmed can only reference the publicly available data from sources such as The Adverse Event Reporting System (AERS). The owner of the NDA for OMNITROPE, Sandoz, Inc., is the stakeholder who is best positioned to address this question.

Regarding patient switching between different growth hormone products, the pre-approval clinical studies of Omnitrope included patients that previously received Genotropin® and were switched to Omnitrope. Over the next 6 months of treatment the rate of antibody positive subjects was unchanged. Therefore in this case there was no

evidence of new safety issues with product switching – even under the carefully monitored scrutiny of clinical study.

The owner of the NDA for OMNITROPE, Sandoz, Inc., is the stakeholder who is best positioned to address the question regarding payers and drug availability.

Regulatory / Administrative

1. Some believe Section 505 of the FFDCA provides a regulatory pathway for approval of biosimilars of 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 should be one regulatory standard for evaluation of FOBs by the FDA. This standard should be the same regardless of if the reference product was approved under the FD&C or the PHS Act.

2. The current status 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?

Yes, the FDA has used its statutory discretion appropriately. Insmed is not aware of a manufacturing change for an FDA approved product that has led to increased safety risks (the manufacturing changes introduced to EPREX (*epoetin alfa*) were for European distribution), and therefore Insmed believes that the FDA's discretion has been adequate to control changes in the manufacture of approved biologics.

3. What FDA office should review FOBs?

Insmed has no view as to how the FDA should internally organize for the evaluation of FOBs.

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 possible"? How would FDA assess these requirements?

In April 1996, the FDA implemented a guidance entitled "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products." This established a standard in which the applicant established the comparability of a product with a precursor product though a combination of analytical studies, biological assays, and, if warranted, preclinical or clinical studies.

This model has served the industry well over the last 12 years. Although these guidelines exist, there is no legal, scientific, or regulatory definition of "comparable". The determination of comparability is made by the scientific experts at the FDA based on data presented by the manufacturer. The determination of similarity for FOBs should be made in the same manner.

Insmed believes that FOBs should be "as similar as scientifically possible" to the reference product insomuch that this does not raise a standard higher than that required for the reference product. The technology available today is vastly more sophisticated than was available for the review of the reference product, and Insmed believes that the FDA should expect the FOB applicant to use state-of-the-art methodology to characterize the FOB.

An FOB applicant bears the responsibility to demonstrate to the FDA by physicochemical characterization, evaluation of product purity, and potency that the biosimilar product is similar to the reference product. The FDA has the scientific capabilities to evaluate the data provided by the applicant to determine if the biosimilar product is of sufficient purity and potency to be similar to the reference product by their expertise in drug and protein evaluation as well as their knowledge of analytical technologies.

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?

No. The FDA does not uniformly apply guidance to different types of products and therefore requiring implementing guidance places a special burden on the FDA as it relates to FOBs. For example, FDA did not issue guidance prior to approving FOBs (e.g. OMNITROPE) through the FD&C Act. Moreover, given the rapid advance of analytical technologies, guidance documents might be outdated before they are issued. Finally, FDA guidance is not all inclusive– it solely represents FDA's current thinking on a given topic. Manufacturers and FDA may choose not to follow guidance, and alternate procedures are acceptable.

Furthermore, Insmed believes that general guidance or even product-specific guidance documents are less useful to an FOB applicant than fact-based assessment and advice based on the FOB applicant's own data. Such case-by-case evaluations permit the applicant and the FDA to resolve the unique issues that are expected to arise during product development.

Insmed does not believe that the FDA should be required to entertain public comment prior to accepting submissions of applications. The FDA has a wealth of knowledge for biotechnology medicines based on over 25 years of products being developed, approved,

and marketed. Such a public process assuredly is an invitation for abuse as a tactic to delay the submission and approval of FOB products.

Finally, Insmed does not have a view as to how long it would take the FDA to implement new regulations and guidance, however Insmed does not believe that promulgating guidance for FOBs is the best use of FDA resources. Issuing guidance documents can be a lengthy process. For example, the FDA issued guidance in February 2008 entitled "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products" that finalized draft guidance of the same title dated January 1998.

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?

Insmed believes that the FDA is best suited to establish the resources required to implement a generic biologics program. Insmed supports the implementation of user fees for the expert review and timely approval of FOBs.

Insmed believes that the eventual approval of FOBs will require a full description of the chemistry, manufacturing, and control section, an abbreviated nonclinical section, and an abbreviated clinical evaluation. Insmed believes that the user fees applied to FOBs should be proportional to the fees applied to traditional drugs in consideration for the abbreviated nature of the nonclinical and clinical sections of the application.

Patents

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

The CRS Report for Congress entitled "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")" dated January 10, 2005 reports that the effective patent term for pharmaceuticals is 11.7 years.

By contrast, two of the most successful biotechnology drugs have enjoyed extremely long patent life due to the patent owner's use of transitional patent term rules enacted as part of the General Agreement on Tariffs and Trade (GATT).

EPOGEN Originally approved to US market 6/1989
Patent family expiration 5/2015 (5,756,349 patent used in litigation)
Patent exclusivity from the time on market = 25 years 11 months

NEUPOGEN Originally approved to US market 2/1991

Patent family expiration 12/2013 (patents listed on the package insert)
Patent exclusivity from the time on market = 22 years 9 months

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 is a good model for FOBs. The lesson we have learned from Hatch/Waxman is that the pharmaceutical industry enjoys product exclusivity that provides a good return on its investments. The US pharmaceutical industry has become a dominant economic force in the United States. Moreover since 1984, there is no evidence that innovation has been stifled by the introduction of generic competition.

The Hatch/Waxman Act provides 5 years of data exclusivity and patent restoration of up to 14 years. Hatch/Waxman does not shield patents from challenge, however, and thus patent term restoration is not an unbreakable assurance of monopoly. By contrast, some stakeholders have requested that biologics enjoy up to 14 years of data exclusivity in addition to the patent term restoration that they can enjoy. As such, these stakeholders are requesting a guaranteed monopoly that is significantly longer than those provided under Hatch/Waxman. The investment required to develop a small molecule and a biologic are roughly equivalent, so there is no compelling financial rationale to support a different period of data exclusivity (DiMasi and Grabowski (2007) Managerial and Decisions Economics 28:469-79).

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?

Patents on biotech medicines have provided significant protection of biotechnology inventions and this will not change if a pathway is created to allow for regulatory approval of FOBs. Granting FDA the ability to define a development pathway for a FOB does not in any way affect the patent rights of the innovator product's manufacturer.

Patents for biotech medicines are comparable to those of small-molecule drugs in the protection that they afford the patent owner. Patents are awarded by the PTO to provide claim scope commensurate with the invention in view of the technological advances and what was known prior to the invention. The small molecule pharmaceutical manufacturers work under the same limitations. Rarely does a pharmaceutical manufacturer enjoy complete dominance over the patent rights for a class of drugs. Instead, once a successful class of drugs is discovered, other manufacturers use innovative science to create similar drugs of the same class that are outside of the patent

rights of the original innovator. If an innovator company fails to secure patents of sufficient breadth to prevent similar products from being developed, it is not the responsibility of the Congress to reward them with an alternative form of monopoly rights. This is the *quid pro quo* of the patent system and the basis for future innovation.

There is evidence that demonstrates that biotechnology patents can be used to keep similar or even different products off the market. Amgen successfully litigated its patents covering EPOGEN against Transkaryotic Therapeutics Inc. (TKT) to prevent market entry of DYNEPO which was similar to EPOGEN but manufactured using a different cell line. Amgen has more recently litigated Roche with some of the same patents to keep an entirely different product, MIRCERA, off of the US market. As such, there is ample evidence that claims of proper scope can be successfully used to prohibit similar products and even different products from reaching the market.

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?

A procedure should be established in which the FOB applicants declare to the FDA a patent certification similar to those established under ANDA rules that can establish:

(1) that the applicant is not aware of any patents to the reference product;
(2) that the patents have already expired;
(3) the date to which the patents will expire; or
(4) that the patents are invalid or will not be infringed by the manufacture, use or sale of the drug for which the FOB is submitted.

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?

Insmed has no view as to how a statutory mechanism should be implemented to balance the interests between third-party patent holders and the reference product sponsor.

6. Should an FOB statute require FDA to administer patent listings 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?

Insmed believes that the FOB statute should adopt the patent listings provisions of Hatch/Waxman except that the patent listings should be updated to require listing of all patents to which the sponsor believes protects their product manufacture, composition, formulation, and marketed use.

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?

Biologics should be given equal treatment as small molecule pharmaceuticals. The data exclusivity provisions of Hatch-Waxman were implemented as a "foundation" monopoly right such that if patent rights were not available for any given product, then the innovator product would have some period of exclusivity to earn rewards for investment. It was not intended to be a replacement to patent rights. If data exclusivity rights are extended to terms nearing those of patent rights, then the motivation to secure patent rights is diminished and innovation will suffer. The *quid pro quo* of the patent system is a time-limited monopoly right in exchange for publishing innovation into the public domain. This serves as the basis for future innovation.

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?

Insmed has reviewed the public assessments published by other stakeholders but has not commissioned its own studies. Insmed believes other stakeholders are better positioned to explain the assessments conducted to support the minimum term of exclusivity that they believe are necessary for the industry. However, we know of no study that supports a period of exclusivity greater than that provided by Hatch/Waxman for small molecule drugs.

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

For biological products, modifications to approved products are generally approved as new products. As such, data exclusivity for the original product should not affect the approval of a modified product and the modified product should enjoy its own data exclusivity.

If data exclusivity for the original product were permitted to block approval of new products, it would have a negative impact on innovation. Examples of modified forms of approved products include pegylated products (such as G-CSF and the alpha interferons) and hyperglycosylated erythropoietin, which was approved as a distinct product from *epoetin alfa.*

Insmed believes that biological products that are modified in such a way that results in different pharmacological/clinical efficacy should be awarded unique data exclusivity. However, Insmed believes that legislation should avoid a mechanism that allows innovator companies to make minor, insignificant changes that allow for "evergreening".

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

The principal benefit of data exclusivity is inherent in the fact that it is an additional form of monopoly right held by the innovator. It often provides an overlapping form of protection in addition to patent monopoly rights. It differs from patent rights in that data exclusivity does not have the "checks and balances" that are built into patent law. Therefore once data exclusivity rights are granted, there are few methods to withdraw the term other than those specifically assigned to the FDA.

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

No. Policies should not be enacted to preferentially reward biotechnology over small molecule drugs. The investment required to develop a small molecule and a biologic are roughly equivalent, so there is no compelling financial rationale to support a different period of data exclusivity (DiMasi and Grabowski (2007) Managerial and Decisions Economics 28:469-79). If a preferential treatment were enacted, it could form the basis for disincentive to invest in research for small molecules.

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

Patents are a time-limited monopoly right granted by the government to an inventor who shares their knowledge as a means to foster innovation. Patent law creates checks and balances on this monopoly right specifically designed to foster further innovation. Creation of substantially equal or superior forms of monopoly exclusivity risks tipping the balance between the rewards of an innovative discovery and inhibiting new innovation.

7. If a follow-on biologics pathway was created without additional incentives – beyond existing patent protection – 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?

The lessons of Hatch/Waxman demonstrated that competition can be introduced into the pharmaceutical market without stifling innovation. There is no reason to believe that a different outcome would occur if competition were permitted for biologics.

Despite arguments to the contrary, Insmed does not believe that new incentives are necessary for continued innovation in the biotechnology sector. The market provides

sufficient incentive for the development of biologic products. Studies have shown that almost 50% of the current clinical development pipeline candidates are biologic products. Such a robust development has occurred without having any new incentives in place.

Finally, research at American universities is almost solely protected and supported by patent protection. Any data exclusivity would only benefit the sponsor of the reference product and not third-party patent holders including American universities. As stated in response to questions 1 and 6, enhancing incentives in the form of data exclusivity may weaken the patent protections of these parties.

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.

In a report published in February 2008, former Undersecretary of Commerce in the Clinton Administration Robert Shapiro found that savings from biogenerics could amount to billions more than previously thought. A follow-on biologics approval pathway could save American consumers, payers and Government more than $370 billion over the next two decades alone. While experts generally believe that it would take approximately two to eight years to implement any new follow-on biologics legislation, depending on the length of clinical trials and the FDA approval process, a follow-on biologics pathway would immediately begin to generate significant savings, especially if the biogeneric is developed before the patent expires.

Earlier studies underestimated the savings from follow-on biologics because experts did not factor in low-cost generic production in other countries such as India, where generic producers are already manufacturing biogenerics. In addition, studies did not account for the increase in the number of biologics users as prices decrease, which increases total savings. Over the first 10 years of biogeneric production (estimated at 2010 to 2019), Shapiro's study estimates a savings of $67.0 billion or $107.7 billion when a 25% discount and a 35% discount over the brand name drug is applied, respectively.

Moreover, Shapiro believes savings could amount to $235.7 billion to $377.7 billion over the first 20 years (2010 to 2029), but he contends that this discount could be much higher. Discounts from traditional generic drugs are estimated at 48% with 2 generic competitors in the market, 56% with 3 competitors, and 67% with 5 generic producers.

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?

Insmed has estimated that the cost to develop four FOB products through approval over the next 10 years is approximately $1.1B including $131M for R&D and $939M for Sales, Marketing, and Administration (including Post-Approval Monitoring).

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

The United States biotechnology industry is at a disadvantage for currently existing under a de-facto monopoly. Other nations have established a follow-on biologics approval pathway, encouraging innovation abroad. Since November 2005 when the European Union (EU) established an approval pathway, the European Agency for the Evaluation of Medicinal Products (EMEA) has approved 5 biogeneric drugs for sale within the EU. The U.S. biotech industry should be permitted to develop follow-on biologics in order to stimulate research, development, price competition and consumer choice. Doing so is essential to ensuring that America's biotech industry remains at the forefront of drug development.

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?

Establishing an approval pathway for follow-on biologics will encourage research in an industry critical to our innovation-based economy. Until now, certain companies within the biotechnology industry have enjoyed perpetual protections for products, some of which have been protected from competition for more than twenty years while costing thousands of dollars per patient. As treatment moves more and more toward specialized medicine, competition will drive the industry toward tomorrow's therapies while enhancing patient access and reducing costs for a healthcare system facing unsustainable expenses.

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?

Reasonable protections for intellectual property are of critical importance for innovators, including Insmed. Insmed is a strong proponent of property rights which ensure that innovation is rewarded. But these protections were never meant to be indefinite, as they discourage these same innovators from investing in better therapies with today's resources.

A follow-on biologics approval pathway must include adequate protections for innovation and patents in order for innovators to recover the cost of research and development and earn a reasonable return on their investment. However, only a truly

reasonable limit on protections will benefit patients, healthcare providers the biotechnology industry itself.

European Model (abbreviated approval pathway)

1. The European Union 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.?

No. The FDA has not required a uniform application of guidance documents to ensure the safety of the patients in the U.S. and there has not been any evidence that this practice has compromised patient safety.

The questions assume that the EU guidances have provided benefits to industry, healthcare providers, and patients. Insmed is not sure that there has been a demonstration of a benefit of guidances versus the outcome if guidances were not available. For example, the GUIDANCE ON SIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT ERYTHROPOIETINS (EMEA/CHMP/BMWP/94526/2005) was established as a draft document in March 2005 and came into effect in July 2006. BINOCRIT is a biosimilar *epoetin alfa* that was developed by Sandoz GmbH. In the Scientific Discussion regarding the approval of BINOCRIT, it was noted that Sandoz was granted a deviation against the guidance regarding clinical studies using subcutaneous administration of *epoetin alpha* because the route of administration was contraindicated while Sandoz was conducting its clinical development of BINOCRIT. (During the evaluation of the PRCA issues with *epoetin alpha*, subcutaneous administration was contraindicated; it was reinstated in May 2006.) Therefore Sandoz initiated its development program before Guidances were in effect and likely well before any drafts were adopted. This demonstrates that Sandoz did not require a guidance to develop this biosimilar product and thus it is not clear that any benefit was derived from its implementation.

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 US be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?

The Article 8(3) of Directive 2001/83/EC provides 10 years of data exclusivity for all medicinal products and does not discriminate between small molecules and biologics. The period of 10 years was determined by the governments and market controls that are in place in Europe. It is noteworthy that Europe has vastly different models of healthcare as well as price controls on their drugs. It would be imprudent to consider the amount of

exclusivity granted to drugs and biologics without considering their impact on the other aspects of the distribution of health care in Europe.

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

The 10 year period of data exclusivity awarded for approval of a medicinal product was determined by the governments and market controls in place in Europe. However, Europe has vastly different models of healthcare as well as price controls on their drugs. It would be imprudent to consider the amount of exclusivity granted to drugs and biologics without considering their impact on the other aspects of the distribution of health care in Europe.

Conversely, the US provides a shorter amount of data exclusivity for therapies but allows market forces to largely drive prices. This model has permitted the pharmaceutical and biotechnology industries robust incentive for innovation.

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?

As stated in response to question 3 above, it is difficult to compare a regulatory model outside of an evaluation of other aspects such as legal systems and health care systems. With regard to US FOB policy, the most appropriate model to consider is US generics policy.

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?

The owners of the NDA for follow-on products approved under the FFDCA or in Europe the MAA are the stakeholders who are best positioned to address this question.

Insmed is not aware of any published evidence of unique safety problems seen with these products compared to their brand counterparts. In fact, when compared to small molecules, biologics, in general, have had a strong safety record.

In 1987 (21 years ago) the first hGH product was approved for the US market. This product was granted Orphan Drug Exclusivity for 7 years. In the mid-1990s, 4 hGH products were introduced to the US market. FDA recognized the highly similar nature of all five of these recombinant protein products by assigning the same established name "somatropin". Each of these products is manufactured with a different manufacturing process, to include different cell lines. For over a decade these products have been marketed simultaneously in the US. Overall, a strong safety and efficacy record has been demonstrated without distinct indications of safety differences among the different products.