DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

SEP 18 2008

Dear Mr. Chairman:

Thank you for your letter dated April 3, 2008, cosigned by Mr. Nathan Deal, Ranking Member, Subcommittee on Health, Committee on Energy and Commerce, regarding a pathway for follow-on biologic (FOB) products. We have restated each of your questions in bold below, followed by our response. Please note that there are several questions that FDA did not address as they do not fall within the Food and Drug Administration's (FDA or Agency) purview.

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 to stimulate an immune response. An immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies to an immune response with significant impact on safety or effectiveness, including the potential to decrease or block the clinical effect of the therapeutic protein. Proteins are more likely to engender an immune response than smaller molecules. Adverse events secondary to immune responses can be life-threatening and include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous protein (e.g., erythropoietin). Immune responses to administered protein products can be life-threatening. Immunogenicity may be influenced by patient-related, disease-related, or product-related factors.

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?**

The ability to predict immunogenicity of a protein product, particularly of the more complex proteins, is limited. We believe that there are few, if any, circumstances that could be envisioned where assessment of immunogenicity would not be critical. Therefore, some degree of clinical assessment for a follow-on biologic's immunogenic potential will likely be needed. The extent of independent testing needed will depend on a variety of scientific factors such as the intended indication, whether the product is to be administered chronically, the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule. As noted above, immune responses to administered protein products can be extremely serious or life-threatening; therefore, this issue requires significant attention and will vary on a case-by-case basis. We believe that such studies must be mandated in statute, while allowing FDA the discretion to determine how much data are necessary for the assessment of immunogenicity.

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?**

FDA believes it has exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes. As outlined in "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products," each manufacturing change and each product may present unique safety, identity, purity, and potency concerns; therefore, the necessary information required for manufacturing changes will vary for different products and for the manufacturing stage at which a change is implemented. Likewise, the International Conference on Harmonization Guidance (Guidance for Industry: Q5E comparability of Biotechnology/ Biological Products Subject to Changes in their Manufacturing Process), notes that when possible adverse consequences of a manufacturing change cannot be excluded, the manufacturer should consider performing clinical studies, especially taking into account the characteristics of the product including the potential for immunogenic responses.

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?**

The manufacturer will need to provide information that justifies the safety and efficacy of their product for each of the requested indications. However, the extent of clinically-derived, *indication-specific* information needed to support the approval of a product for multiple indications will depend on a number of factors. These include how well the mechanism of action of the FOB is understood, how well delineated are the established benefits and toxicities in each of the clinical settings, and the relationship between the product's physiochemical characteristics and its clinical activity.

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?

The postmarketing authorities enacted under the Food and Drug Administration Amendments Act of 2007 should be applied to FOBs in a manner comparable to other drugs and biologics. The need for postmarketing studies will be dictated by the contents of the application – what is known and what is not known. There may well be circumstances under which FOB applicants will need to conduct postmarketing studies. This may depend on what has previously been elucidated about the marketed product or may stem from identifiable differences between the two products.

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?**

FOBs also present issues with pharmacovigilance (for example, post-market surveillance and withdrawal based on class or specific product concerns). Currently, all products are assigned an International Non-Proprietary Name (INN). This is highly relevant in the context of biosimilars, given that these products would be considered similar, rather than the same. FDA recognizes the complexity of developing a policy on non-proprietary naming of FOB products. Any such policy will need to consider potential impacts on the non-proprietary names of products currently on the market. FDA believes that legislation should recognize the potential impact on pharmacovigilance and prescribing and require that these products be assigned a distinguishable, non-proprietary name for safety purposes. FDA's paramount concern is that patients not be exposed to an avoidable safety risk by being switched to a product not known to be interchangeable with the product they are currently receiving.

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?**

It is imperative that the reference product and the FOB have the same mechanism of action. In the case where the mechanism of action of the reference product is unknown, there will be greater uncertainty regarding the potential clinical significance of any structural differences between the reference product and the FOB. Any such uncertainty may need to be resolved via clinical studies. If the mechanism of action is known to be different, then the product cannot be considered to be a FOB.

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?**

For individual brand protein products, the degree of variability in chemical structure from batch to batch or as a result of a manufacturing change depends on many factors, including the following: 1) the complexity of the product in terms of higher order folded structures and post translational modifications (e.g., glycosylations), as well as number of active components in the product; 2) the demonstrated robustness of the product's performance to structural variations; and 3) the impact of the manufacturing change on structural variability (e.g., the change may decrease variability). It is not possible to provide a single measure of variability that would be representative for all protein products.

With respect to interchangeability, a key aspect of generic drugs is that their chemical composition is the same as the innovator drug. Products approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), i.e., generic drugs, may be designated as therapeutically equivalent to the reference product, and thus considered "substitutable" or "interchangeable." Under State law, such products may be substituted for the reference product by a pharmacist, which may provide for cost savings.

However, protein products are more complex and are frequently immunogenic. The impact of immunogenicity can be serious and life threatening. In most cases, follow-on protein products will not be the same as the reference product in the manner that generic drugs approved under section 505(j) of the FD&C Act are the same as the listed drug. In addition, even if a follow-on protein product is determined to be biosimilar to the reference product, immunogenicity could preclude patients from switching from one product to another.

Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products. Scientific and safety issues of determining interchangeability at present are significant, including for pharmacovigilance (for example, postmarket surveillance and withdrawal based on class or a specific product).

For many follow-on protein products, there is a known significant risk in repeatedly switching between products and a resulting negative impact on both patient safety and/or effectiveness. Pharmacies or patients might substitute biological products determined to be biosimilar, but not determined to be interchangeable for one another, possibly resulting in serious injury or death. Therefore, while there may be the possibility of determining interchangeability in the future, in light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, the Agency believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician.

As noted in the response to question 6, above, any policy on non-proprietary naming of follow-on protein products will need to consider potential impacts on the non-proprietary names of products currently on the market.

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?

Applicants submitting a Biologics License Application (BLA) under section 351 of the Public Health Service Act (PHSA) are generally required to perform one or more clinical studies to establish that a biological product is safe, pure, and potent. FDA believes that legislation should require that sponsors of follow-on products meet the same high standards for approval as reference biological products. In order to meet this standard, the data needed to demonstrate that a product is safe, pure, and potent will depend, among other things, on the specific biological product at issue. For instance, the extent of clinical information required depends on how much is known regarding mechanism of action, degree to which structural similarity could be assessed, comparative pharmacokinetic and pharmacodynamic data, and immunogenicity. Given the current level of understanding, at least some clinical information will be needed to assess the safety and efficacy of most FOBs. Legislation should require clinical trials, but FDA should be given discretion to determine through a transparent and public process what clinical trials are needed to support the licensure of a FOB.

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?

In general, the amount and type of new clinical (human) data required for approval of a follow-on protein product will be influenced by the extent to which the follow-on product can be demonstrated to be sufficiently similar to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product. For example, the approval of Omnitrope, a recombinant human growth hormone, in 2006 was based on comparative physicochemical, bioactivity, pharmacokinetic, pharmacodynamic, and clinical data (including immunogenicity data) demonstrating, with bridging across drug substance and formulation changes, that Omnitrope is highly similar to Genotropin, a previously approved recombinant human growth hormone. Although Omnitrope was approved in part in reliance upon FDA's finding of safety and effectiveness for Genotropin, Omnitrope has not been determined to be therapeutically equivalent to, and thus substitutable for, Genotropin.

We also have approved small (e.g., eight amino acid) synthetic peptide products under the abbreviated new drug application pathway at section 505(j) of the FD&C Act without clinical safety or effectiveness data.

At this time, we have not approved a recombinant protein (as distinguished from a synthetic or naturally-sourced protein) through the 505(b)(2) pathway without clinical trials (other than bioavailability or bioequivalence).

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?

FDA's Center for Drug and Evaluation Research (CDER) conducted a search of the Adverse Event Reporting System (AERS) database through April 22, 2008, and identified two reports of adverse events submitted with regard to Omnitrope. Both were foreign reports. One report involved a 12-year-old boy with a history of growth hormone deficiency who experienced snoring and adenoidal hypertrophy (enlarged adenoids) two weeks after starting Omnitrope. The other report involved a 9-year-old girl with a history of Turner's syndrome who experienced thrombocytopenic purpura (a bleeding disorder characterized by low platelet count) about three years after starting Omnitrope. Based on these two reports in AERS, we cannot make any conclusion regarding Omnitrope-related adverse events.

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

FDA has not determined that Omnitrope is therapeutically equivalent to, and thus substitutable for, any other sponsor's recombinant human growth hormone product. It is possible, however, that patients could be switched between recombinant human growth hormone products by a physician or other health care provider. Omnitrope is not therapeutically equivalent to any other human growth hormones but it is an alternative treatment option. CDER examined total dispensed prescriptions (new and refilled) for somatropin products using Verispan, LLC: Vector One®: Prescription Services (VONA/VOMA) for year 2007. These estimates do not include products dispensed from home health care pharmacies, which represents roughly a third of the wholesale distribution for somatropin. Presently, FDA does not have access to databases that can provide an estimate of dispensed prescriptions from these channels. The following information was noted as a result of database queries:

- In 2007, 195,501 new and refilled prescriptions for somatropin products were dispensed from retail and mail order pharmacies in the U.S. Omnitrope represents less than 1 percent of the somatropin market share for dispensed prescriptions.

- In 2007, an estimated 1,565 new and refilled prescriptions for Omnitrope were dispensed by retail and mail order pharmacies. Of these, less than 5 percent (69/1,565) of prescriptions were from patients who had previously received another Anabolic Hormone prescription within the previous 6 months AND also had a different brand dispensed in the same defined class of Anabolic Hormone for the past 6 months (switch/add-on activity[1]). Of new Omnitrope prescriptions dispensed, when a patient was either switched to Omnitrope or when Omnitrope was added to the patient's current

[1] Switch activity is when the patient is switched from one brand of the drug to another. Add-on activity is when a patient remains on one brand while therapy with another brand is added.

therapy, around 78 percent (35/45) of the previously used products were other somatropin products.

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

FDA does not have access to information on how payers are handling the availability of Omnitrope.

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?

FDA has approved some follow-on protein products under section 505(b)(2) of the FD&C Act. However, this is only for protein products where the innovator products are regulated and were approved as drugs under section 505 of the FD&C Act. The majority of protein products have been licensed as biological products under the PHSA. Currently, the PHSA does not contain an abbreviated approval pathway for biological products licensed under the PHSA that is analogous to the abbreviated approval pathways under sections 505(b)(2) or section 505(j) of the FD&C Act.

We believe that any proposal to transfer certain products now regulated under section 505 of the FD&C Act to section 351 of the PHSA should not be undertaken without very careful consideration of the legal and policy implications of such a change on the regulation of these products. For example, insulin products are proteins that have been regulated under the FD&C Act for more than 60 years. There could be significant regulatory implications if this product class were now to be approved or licensed and regulated under the PHSA. The Agency has not completed its considerations of this issue and would want to fully consider the potential implications of any specific proposal.

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?

FDA believes that the current statute that gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial is adequate and appropriate.

3. What FDA office should review FOBs?

Follow-on protein products will be reviewed by the same office in which the original approved product (the reference product) was reviewed.

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?**

FDA believes that product-class guidances should be developed to outline what would be considered to be "highly similar" for the purposes of that specific class of products. This would ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the Agency has optimum information regarding safety and efficacy considerations for follow-on products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content.

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?**

FDA believes that requiring a predictable and public product-class guidance process prior to acting on any follow-on applications would be beneficial. This process should ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the Agency has optimum information regarding safety and efficacy considerations for follow-on protein products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content.

The timeframe within which a regulatory framework, including new regulations and guidances for FOBs, could be established would depend upon the requirements of enacted legislation, the complexity of the product class, the volume of comments received through a public process, and the availability of Agency resources.

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?**

To review follow-on applications, FDA will need additional resources. Although FDA has not yet had the opportunity to consider the full costs likely to be associated with the review of follow-on applications, FDA believes that these applications will require approximately the same resources initially as comparable BLAs and NDAs. In addition, there will be "start up" resources needed to launch the program.

In addition, in light of the importance of ensuring the timely review of safe and effective generic drugs, the Agency believes it is vital to authorize the collection of user fees for review of generic drug applications under section 505(j) of the FD&C Act consistent with the President's FY2009 budget.

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?**

Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products. Scientific and safety issues of determining interchangeability at present are significant, including for pharmacovigilance (for example, postmarket surveillance and withdrawal based on class or a specific product).

To establish that two protein products would be therapeutically equivalent (interchangeable), a sponsor of the follow-on protein product would need to demonstrate, among other things that repeated switches from the follow-on protein product to the referenced product, and vice versa, would have no negative effect on the safety and effectiveness of the products. It is likely that the manufacturer of a follow-on protein product would have to conduct clinical studies evaluating such switching before a claim of interchangeability would be permitted. The design and ethical considerations for such studies will require careful consideration. In light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, FDA believes that patients should not be switched from the reference biological product to a follow-on biological product (or vice versa) unless directed to do so by their physician, and legislation should not allow for determinations of interchangeability at this time.

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

In general, demonstration of interchangeability would be based on, among other things, a showing of similar relevant structural characteristics between the two products, an understanding of the structure-function relationships, and clinical data evaluating the impact

of switching patients from one product to the other. There may be a need for standards to ensure structural similarity and interchangeability over the products' lifetime.

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?**

As previously discussed, there is a known significant risk in repeatedly switching between products and a resulting negative impact on both patient safety and/or effectiveness. While there may be the possibility of determining interchangeability in the future, pharmacies or patients might substitute biological products determined to be biosimilar, but not determined to be interchangeable for one another, possibly resulting in serious injury or death. Therefore, in light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, the Agency believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician, and legislation should not allow for determinations of interchangeability at this time.

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

As noted in the response to question number 5 under the Regulatory/Administrative section, above, FDA believes that the implementation of a public product-class guidance process prior to acting on any follow-on applications would be beneficial.

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 pharmacist? Why or why not? How would interchangeability affect patient access to biologics?**

As noted in the response to question number 1 under the Science/Safety section, above, an immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies to an immune response with impact on safety or effectiveness. Adverse events from an immune response could include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous protein (e.g., erythropoietin). Immune responses to administered protein products can be life-threatening. Immunogenicity may be influenced by patient-related, disease-related, or product-related factors. Thus, without clinical evidence that patients can be switched back and forth between two products without any detrimental effect, such changes should not be made unless directed by a physician, and legislation should not allow for determinations of interchangeability at this time.

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

We believe that the complexity of the interchangeability issue would preclude reliance on a paradigm analogous to the generic drug model. We cannot speculate about the impact on pricing or health plans.

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?

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 patent term restoration provisions of the Hatch-Waxman Act, which restore up to 5 years of the term of an unexpired patent but which cannot result in a patent term longer than 14 years from the date of product approval, currently apply to biological products licensed under the PHSA (see 35 U.S.C. 156). The statute addresses, among other things, "a patent which claims a method of manufacturing the product which primarily uses recombinant DNA technology in the manufacture of the product..." (35 U.S.C. 156(a)(5)(B)). However, the 5-year exclusivity provision of the Hatch-Waxman Act applies only to drug products approved under section 505(b) of the FD&C Act (see section 505(c)(3)(E)(ii) of the FD&C Act).

The lessons learned from the Hatch-Waxman Act lead the Agency to believe that, to ensure continued innovation, legislation authorizing a follow-on biological pathway should include incentives to develop innovative biologic products. The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies). Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

3. Please explain if patent 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?

FDA's role in administering the patent listing provisions of the Hatch-Waxman Act and ensuring compliance with patent certification requirements is purely ministerial.

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?**

The Agency does not have a position on the procedures that should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims related to FOBs. We note, however, that even FDA's limited current role in administering the patent listing provisions of the Hatch-Waxman Act and ensuring compliance with the patent certification requirements can embroil the Agency in litigation. The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation.

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?**

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?**

As stated in the response to question 4 above, the Agency does not have a position regarding whether the Hatch-Waxman patent listing and notification process would be appropriate for an FOB statute.

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?**

The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves, a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies).

Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact 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?

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

An additional exclusivity period should be provided if, during the period of exclusivity, the sponsor of the reference product submits and FDA approves, a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies).

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

A clearly-defined period of exclusivity provides certainty to reference product sponsors. Patent protection differs in that patents may be challenged by a follow-on protein product sponsor as invalid, unenforceable, and/or not infringed.

5. Do you think biologics should receive a different period of data exclusivity than drugs?

The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of exclusivity protection to ensure continued innovation.

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

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?

Innovation would be negatively affected by the creation of a follow-on biologics pathway without additional incentives beyond existing patent protections. Not all biologics are protected by a patent, and even if there is a patent the cost of litigating patent issues are significant. The cost of establishing that an original biologic product is safe and effective is high. Because a sponsor who developed the innovative biologic may not be able to obtain funding to do the necessary research if they cannot expect to recover the cost if the biologic is approved, additional incentives should be provided to encourage research into the safety and efficacy of biologics. The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves a BLA supplement for a new indication for which new clinical studies were required

(other than bioavailability studies). Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

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.**

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?**

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

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?**

In general, a FOBs approval pathway may be expected to reduce the barrier to market entry for a follow-on product once a patent that claims the reference product expires. However, it is difficult to evaluate the implications of the treatment of patents in the context of a follow-on biological approval pathway outside of the context of other incentives for biotechnological innovation such as exclusivity protection, which may be coextensive with a significant portion of the term of a patent that claims the reference product.

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 Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of exclusivity protection, independent from any patent protections that might be applicable to the product, to ensure continued innovation.

European Model (abbreviated approval pathway)

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.?**

The Agency believes that a predictable and public product-class guidance process should be required prior to acting on any follow-on applications. It should ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the Agency has optimum information regarding safety and efficacy considerations for follow-on products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content.

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?**

As noted above, the Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of exclusivity protection, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves, a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies). Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

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?**

The Agency has not undertaken an analysis of the effects of the European Union's current model (or other approaches) on access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for the approval of a new product, and therefore is not able to comment.

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?

FDA has not done a systematic review of all of the follow-on protein products approved under the FD&C Act. In general, FDA does not distinguish postmarket surveillance of brand products from follow-on or generic products. However, FDA's MedWatch Program is an important tool that captures safety information and adverse event reports and helps FDA monitor the safety of all medical products regulated by FDA.

Thank you for contacting us concerning this matter. Please let us know if you have further questions. The same response has been sent to Ranking Member Deal.

Sincerely,

Frank M. Torti, M.D., M.P.H.
Principal Deputy Commissioner
and Chief Scientist

cc: The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce

The Honorable Joe Barton
Ranking Member
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