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 an undesired immune response to a drug. Immunogenicity is a special concern for biologics because, unlike chemical drugs, biologics are proteins that can often be recognized as foreign to the body by the immune system. Immunogenic risks to patients include hypersensitivity or allergic reactions to a drug; a decrease in the drug effect or potency due to the immune system neutralizing the drug or removing the drug from circulation; prevention of the body's own protein activity resulting in long term injury or death. Immunogenic risks vary depending on the type of biologic.

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?

For proteins, manufacturing quality often determines the degree of immunogenicity of the drug. Therefore, immunogenicity testing through clinical trials is absolutely necessary and should be mandated for all follow-on biologics, as there is currently no way to predict whether a protein will cause an adverse immunogenic response. Discretion could be applied to the design and duration of such studies, but some studies are absolutely necessary.

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

In our experience, FDA has exercised appropriate discretion regarding whether to require immunogenic testing for innovator manufacturing changes. In the case of an innovator product, FDA can determine whether pre-clinical and clinical tests, including immunogenicity testing, are necessary depending on the extent and nature of the manufacturing change and the experience of the manufacturer with the process and the product. In the case of a follow-on biologic, both the process and the product will be completely new compared to the reference product and therefore immunigenicity testing for the follow-on product should be required. FDA's requirements for the comparison of products before and after a manufacturing change by the same manufacturer should be different from the requirements for a product produced by a different manufacturer with different cell lines and different manufacturing processes.

Our product AVONEX is often discussed in this context. In a Phase III clinical trial, Interferon beta-1a (manufactured in Germany) was shown to be a safe and effective

therapy for MS patients. However, due to unknown structural properties of the drug, about 25% of the patients receiving Interferon beta-1a developed antibodies that neutralized the activity of this drug. As part of the process of moving the manufacture of Interferon beta-1a to the USA (to secure a controlled and adequate supply), numerous changes were made in the manufacturing and purification processes. As a result of this manufacturing change, the presence of neutralizing antibodies was reduced to 5%, as noted in the AVONEX® Prescribing Information.

In order to substitute AVONEX® for the Phase III drug, the FDA appropriately required extremely extensive testing that to a large extent, relied upon the "institutional knowledge" of the chemical properties, animal studies and human clinical trials of the Phase III Interferon beta-1a compared to AVONEX®. Tests included side by side comparisons of the Phase III material with the proposed commercial material. Only the originator would have access to the entire set of development/historical data and the material for these comparisons.

Even with all the proprietary, "in-house" knowledge and experience on AVONEX®, Biogen did an 18 month safety and immunogenicity study with the new material. (This study was extended for a total of 6 years.) Only after the results of this 18 month study in MS patients were available did Biogen and the regulatory agencies know that some of the manufacturing changes had reduced the immunogenicity of the product.

Thus, when the FDA approved the AVONEX® for commercial use, the Agency:

- Required very detailed and comprehensive (perhaps the most ever required) side-by-side comparisons of the Phase III drug with the commercial drug using tests that examined both the biochemical and many functional properties of the Interferon beta-1a.
- Required substantial toxicology/safety studies. Since both forms were Biogen's, the original toxicology studies could be compared as well.
- Required a human study where the PK/PD of the old and new versions were compared.
- Had been apprised of the results of an 18 month long term safety and immunogenicity trial in humans.
- Required extensive Phase IV clinical testing (in MS patients) that would reaffirm the efficacy and safety of AVONEX® in MS in 2 and 3 year studies.

The case of AVONEX® demonstrates that only access to developmental and historical characterization combined with confirmatory safety and immunogenicity data can provide insight in product comparability. Unlike small molecules, protein drugs are too large and complex to understand fully cause and effect with regard to structure/function.

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

FOB applicants should have to provide evidence of similarity, safety, and efficacy for each indication to the same extent provided by the innovator. Extrapolation to separate indications should only be allowed when the mechanism of action is fully understood and maintained in the FOB and only when exposure correlations are clearly understood in the specific population to be treated. The clinical effect of a biologic may vary in different patient populations and may be different for a follow-on product; thus a product that is biosimilar on one indication might not be biosimilar in another.

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?**

Post-market safety requirements should be applied to FOBs according to the same guidelines as they are to other products. There may be situations in which FOB applicants would need to conduct post-market studies that are different from those required for the reference product, because the FOB might have a different safety profile from the reference product, since it will be similar but not the same. Since FOBs will be approved based on abridged clinical trials of shorter duration, the safety follow-up for FOBs might need to be more extensive than that required for the innovator product. In addition, a FOB may be used either as a first treatment for naïve subjects and/or for those who are being switched from an innovator product to a FOB. The Adverse Events in these distinct groups should be tracked separately.

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 should have different non-proprietary names from the reference products. Since the FOBs will be similar but not the same, it is important that they have a distinguishable name so that physicians, patients, drug safety authorities and others can differentiate between the FOB and the innovator product. The benefits of a distinct name is the ability for allow for informed choices by physicians and patients. In our view any alternative creates the potential for unnecessary safety risks and confusion among patients and providers.

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

Yes, it is essential that an innovator product and a FOB are demonstrated to have the same mechanism of action, whenever possible. Two products that are known to have different mechanisms of action cannot be considered sufficiently similar to support a determination that one is biosimilar to the other. When the mechanism of action of the reference product is not known, there is an increased risk that a follow-on biologic will be different from the innovator in a subtle way that has significant clinical consequences for patients. In such cases other types of data must be submitted by the applicant to mitigate the increased risk.

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?**

The variability in chemical structure depends on the process capability of the manufacturer. As experience with the process increases, the variability between batches decreases. The best, consistently achievable results are used for setting quality specifications. In the case of manufacturing changes, the intent is to match the specifications of key product attributes of the new product to known attributes of the product prior to the change. This is done by assessing pharmacokinetics and pharmacodynamics. The innovator manufacturer has significant experience with the product and understands the limits within which those key attributes should fall following a manufacturing change. FOB manufacturers will not have the experiential database of information on the product dating back prior to the earliest clinical trials.

By definition, FOBs are made in a different facility using different processes and cell lines from the innovator. The quality specifications are, therefore different from the innovator product and some level of clinical testing of the FOB product should be required to ensure that it is sufficiently similar to the reference product. Analytical testing alone cannot detect relevant biological variations between the innovator product and the FOB. Since the FOB product will not be the same as the innovator, it should be given a different name. And the FOB product should not be dispensed to a patient without expressly being prescribed by a physician.

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?**

Human clinical trials should be mandated for all FOBs. FDA can be given discretion on the duration and size of the trials depending on the product class and what is known about the reference product. Such discretion can be exercised through the issuance of product-class specific guidance by the FDA. Lack of clinical trials for FOBs will leave the product without established safety and efficacy data, slowing market acceptance of the product and exposing patients to unnecessary but potentially serious health risks.

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?

We do not have any products approved under section 505, so we have no comment on this question.

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

- **Have patients experienced any problems?**
- **Have patients been switched to Omnitrope from other recombinant human growth hormone products?**
- **If the answer to part b is yes, how are payers handling the availability of this comparable product?**

Omnitrope is not our product, therefore we have no comment on this question.

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**?

A newly-created FOB approval process should focus on all biological products to ensure consistent processes and requirements across products.

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?

We believe that the current statutory discretion regarding whether to require a clinical trial for a change or changes made by a sponsor to their product has been appropriate and adequate. It has allowed FDA to base their decisions on scientific data that is unique to the individual product. Patient safety and overall public health have not been adversely impacted by allowing FDA this discretion. Both the FDA and the innovator manufacturer have significant data and experience with an approved biologic at the time that any change is made – including original clinical trials results – and therefore have the background data necessary to evaluate the need for additional clinical trials. Manufacturing changes made by the products manufacturer allow for extensive side-by-side testing of product before and after the change.

3. What FDA office should review FOBs?

The FDA office that reviews the FOB application should be the same office that reviewed the reference product. Biologics are complex products and each product may have unique characteristics that are best understood by the office that approved the innovator product.

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?

FOB manufacturers should be required to adopt the same rigorous scientific standards and analysis as the reference product manufacturer. The FOB should be required to be "as similar as scientifically possible." This standard would establish that the FOB manufacturer has tried in good faith to utilize the most rigorous state of the art scientific methods available to understand the FOBs characteristics. The differences between the FOB and the reference product should be minimized to the extent possible.

The exact meaning of the standard "as similar as scientifically possible" should be further defined by FDA through product-class guidance issued by the agency for public review and comment.

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 should develop guidance documents outlining their criteria for approving FOB applications prior to reviewing applications, as has been done in Europe. This process will ensure that the same standards and criteria are used to assess applications. The process will also enable stakeholders to understand FDA's approval criteria by removing ambiguity and clarifying expected standards. If FDA is to approve these products, then developing guidance outlining how such approvals will be handled is a necessary first step. The issuance of such guidance will enable FDA to gain consensus from stakeholders on the FOBs approval strategy and may help to highlight subtler specifics for each product.

FDA can better comment on the time it would take to put this framework in place.

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**?

In order to accommodate the level of review that will be required to evaluate whether a FOB is as similar as scientifically possible, FDA will need similar appropriations and/or user fees as they have now for innovator biologic products. We believe it is important that any new follow-on biologics reviews/approvals not divert existing resources from the approval of innovative medicines.

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?

Current science does not support substitutability of FOBs for reference products. Since the products will be similar but not the same, switching between the reference product and the follow-on product(s) could have significant patient safety consequences. FOBs should be provided to a patient only when expressly prescribed by a physician.

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

Physicochemical and biological comparability studies, safety assessments, and appropriately designed clinical trials of sufficient size and duration, including crossover clinical studies, would all be required to determine interchangeability. Specific criteria for demonstrating interchangeability should be outlined by FDA in a guidance document available for public review and comment.

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.

Product specific requirements and the criteria for deciding and declaring interchangeability should be laid out in FDA guidance to allow for input from all stakeholders. To the extent that FDA is given the authority for determining interchangeability, they must provide clarification of the circumstances under which such authority will be used along with the scientific rationale for making an interchangeability determination.

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

Yes, there should be product-specific guidance documents, with opportunity for public comment, regarding interchangeability. Such a process would provide for transparency of intent, an increase in the alignment of scientific opinion, the application of adequate scientific rigor, and an open discussion of scientific concerns.

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

The risks involved with interchangeability include the potential change to the safety and/or efficacy of the product. An immunogenic reaction could compromise a patient's ability to receive and be treated with the same class of drugs in the future. Any finding of interchangeability needs to be established through clinical trials designed to meet FDA's requirements for such a finding. These requirements should be established through a guidance process that is open to public comment. If a FOB pathway is designed in such a way to protect patient safety, then such a pathway – with or without interchangeability – should increase patient access to biologics.

In all cases, dispensing of a FOB should only occur with the knowledge and consent of the prescribing physician and the patient. The only way to accurately track and monitor adverse events once a product is on the market is if the physician, the patient, and the pharmacists are all aware of which product was dispensed to the patient.

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

Interchangeability would increase price competition in the marketplace. A well-constructed FOBs pathway should lower the overall cost of biologics. However, an ill-conceived FOBs pathway might provide short-term gain on the cost of biologics, but over the longer term would likely expose patients to unnecessary and harmful risks and would slow the pace of innovation for new therapies to address unmet medical needs.

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?

Several credible studies have indicated that it takes 10 – 15 years to bring a new chemical entity (NCE) from the laboratory to the pharmacy. (See the 2001 report by the Tufts

Center for the Study of Drug Development). Biogen Idec's experience has been in line with these studies, as outlined in the table below:

Drug Name	First Patent Filing	BLA Approved	Discovery to Approval
AVONEX®	October 1980	May 1996	>15 years
RITUXAN®	January 1987	November 1997	>10 years
AMEVIVE®	March 1991	January 2003	>11 years
TYSABRI®	September 1989	November 2004	>15 years

In 1998, the Congressional Budget Office found that the average period of time for marketing of a drug product with patent protection was 11.5 years. A more recent, peer-reviewed study found that new molecular entities are marketed in the U.S. for an average of 13.5 years before the entry of generic competition. (Grabowski and Kyle, 2007)

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 reached a balance between incentives for innovation and entry of generic products to the marketplace. A similar balance must be struck for biologics; yet given the more complex nature of protein products, the mix of tools to achieve this balance must be different. Biologics require a longer data exclusivity period to ensure sufficient incentives for investment; we believe a 14 year data exclusivity period – with a patent dispute resolution system to run during that time – strikes the right balance for biologics.

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?

The scope of patents covering both small molecule and biologic products are defined at least in part by the chemical structure of the drug. The far greater structural complexity of a biologic drug offers competitors with many possibilities for introducing insignificant structural changes to the drug which have little or no impact on activity (efficacy or safety) but which may be sufficient to circumvent the scope of the innovator patent. Given the narrowness/limitations of biologic drug patents, data exclusivity is potentially the more meaningful form of intellectual property protection.

In the case of small molecule drug, generic versions are approved on the basis of "sameness". A standard of "sameness" makes a finding of a patent violation easier to determine. Thus patents provide a greater degree of intellectual property protection for

small molecule drugs in the context of generic competition. In the case of small molecule drugs, data exclusivity and patent protection together form a period of exclusivity prior to generic composition that far exceed the 5 years of statutory data exclusivity (Grabowski and Kyle, 2006).

In the case of a follow-on biologic, the standard is "similarity," not sameness. In such cases, a product might be similar enough to allow FDA to rely on the previously submitted innovator data to find the follow-on product to be safe and effective, but the product might have been designed in such a way that it does not specifically violate the patents governing the product. Thus both patent protection and data exclusivity are critical intellectual property protections for biologics, while patents alone are not sufficient.

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 mechanism should be provided that compels information disclosure from the FOB applicant to the innovator and the third-party patent holders so that each can assess whether or not their patents cover the FOB or its manufacturing processes.

When a FOB application is received, the FDA should issue a public notice. Then any party that believes the FOB product could infringe on its patents should have the right to obtain confidential access to a copy of the FOB application and supporting information on methods of production, in order to identify with particularity potentially infringed-upon patents. There should be a defined window of time provided for such information disclosure and for dispute resolution (including litigation, if needed) set to begin within a reasonable period of time before expiration of the data exclusivity period. The patent dispute resolution system could be designed to run concurrently with the data exclusivity period, which we believe should extend for 14 years.

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?

Through the public notice process outlined above, each relevant patent holder should receive adequate and timely notice of a FOB application, with sufficient information upon which to make a judgment as to whether its patents may be implicated by such application. This process will enable to independently assert its patent rights.

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**?

The public comment mechanism outlined above does not require an Orange Book style of listing maintained by the FDA or any other use of FDA resources or expertise.

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?

Innovator manufacturers should be provided a period of data exclusivity. We believe that 14 years of data exclusivity is required to provide sufficient incentives for innovation. We believe that patent disputes can be resolved within this 14 year timeframe, rather than subsequent to it.

Note that data exclusivity is not the same thing as market exclusivity. Data exclusivity refers to the period of the time during which innovator companies have exclusive use of their proprietary data generated to support a finding of safety and efficacy of a product by the FDA. Market exclusivity provides a product exclusive access to a market (as under the Orphan Drug Act). Multiple products can compete in the same market space under current law, assuming they each submit a complete BLA to the FDA with all necessary data, and assuming the FDA finds each product to be safe and effective in its own right. (See the current market for beta interferon).

Follow-on biologics manufacturers will, by definition, gain approval for their product by relying at least in part on FDA's prior finding of safety and efficacy of an innovator product, which was based on that innovator's propriety data. Data exclusivity refers to the period of time during which only the innovator can rely on their proprietary data, and no other manufacturers can rely on that same data to seek FDA approval with an abbreviated application. As noted above, we believe 14 years is the appropriate time period for data exclusivity.

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?

Henry Grabowski at Duke University has conducted studies on the period of time required to provide incentives for innovation. According to these studies, in order for a robust industry for the discovery and development of biologics to exist, companies must be certain that they will have adequate time to recoup their substantial R&D costs (on average $1.2 billion to bring a biologic to market). The breakeven point for a biologic occurs after it has been on the market between 12.9 and 16.2 years.

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

A second generation product that requires a full BLA and rigorous FDA review should be afforded the same data exclusivity as an original innovator product.

If an approved product is subsequently approved for a medically significant new indication during its original period of data exclusivity, the innovator should be granted a limited additional period of data exclusivity as an incentive to conduct additional research on existing molecules. Similarly, approval of a pediatric indication should also result in the granting of a limited period of additional exclusivity. Such additional periods of exclusivity will encourage additional research into additional applications for existing products.

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

Innovator companies make choices about what they choose to patent and what they choose to maintain as proprietary data or trade secrets. Both forms of intellectual property are important to innovator companies. Patents provide a period of exclusive use to an invention in exchange for telling the world about that invention. Alternatively, companies may develop inventions or know-how that we choose to keep proprietary. Biologic products are incredibly complex; the core protein might be governed by a patent, while the processes for deriving that protein and creating the final product might be governed by proprietary trade secrets. Both the final product and the processes for making it are part of a BLA submitted to the FDA for approval. Thus when companies submit a BLA to FDA, the product is covered by a combination of patents and proprietary data. Data exclusivity serves to protect the proprietary data.

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

Yes, biologics should receive a different period of data exclusivity than drugs. In the case of small molecule drugs, generic versions are approved on the basis of "sameness". A standard of "sameness" makes a finding of a patent violation easier to determine. Thus patents provide a greater degree of intellectual property protection for drugs in the context of generic competition. In the case of drugs, data exclusivity and patent protection together form a period of exclusivity prior to generic competition that far exceeds the 5 years of statutory data exclusivity (Grabowski and Kyle, 2006).

In the case of a follow-on biologic, the standard is "similarily". In such cases, a product might be similar enough to allow FDA to rely on the previously submitted innovator data to find the follow-on product to be safe and efficacious, but the product might have been designed in such away that it does not specifically violate the patents governing the product. Thus both patent protection and data exclusivity are critical intellectual property protections for biologics. We believe a data exclusivity period of 14 years, with a patent dispute resolution system that operates during such time rather than after it ends, provides a comparable period of data exclusivity to that provided to small molecule drugs through patents and data exclusivity under the Hatch-Waxman Act.

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

Both patents and proprietary data are important forms of intellectual property protection for innovator biologics. Please see the answer to question #4 above.

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?

If a follow-on pathway was created without any data protection for innovator products, beyond current patent protections, innovation would suffer. Development of biological products is a long-term, expensive, and risky undertaking. Products can take 10 to 15 years to develop, with an investment exceeding $1 billion dollars, and significant risk of failure. Innovator companies require a period of data exclusivity during which they can recover their investment in a product and secure sufficient returns to conduct the additional research and development that drives innovation. Furthermore, without the ability to generate returns, venture capital and other forms of investment will move away from the biotechnology industry and seek out other avenues for investment. Continued research and innovation requires a period of data exclusivity, not just patent protection, due to the importance of both of these forms of intellectual property protection to the biotechnology industry.

Economic Impact

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

We defer to analysis by BIO and others regarding anticipated savings from FOBs.

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?

Based on our current long-range plan, we expect to spend $13 billion over the next 10 years on biological products.

If FOBs are approved by FDA as similar to the brand name product (but not identical like the small molecule generics), we expect that there would be a 10-20% cost reduction as a

result of the follow-on product. This is due to the significant investment in non-clinical and clinical testing (to ensure patient safety) and complex manufacturing that a follow-on biologics producer would have to make as compared to a small molecule generics company.

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

A well-designed FOBs pathway that ensures patient safety and provides appropriate incentives for innovation will have a positive effect on U.S. economic competitiveness and leadership. However, a poorly-designed FOBs pathway that reduces incentives for biotechnology innovation or undermines intellectual property protection would disproportionately harm the United States, and undermine U.S. leadership in strengthening the protection of intellectual property rights around the world.

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?

As noted above, it is important that the patent treatment be considered in conjunction with a follow-on biologics approval pathway. The pathway must provide sufficient notice and time to resolve patent disputes prior to the launch of the follow-on product. In addition, given that many core patents may technically reside with universities who licensed their rights to innovators, the legislation must provide enough time for all concerned patent holders to defend the patents a follow-on biologics producer wishes to litigate. Without this there will be limited protection for innovation.

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?

If ample incentives for innovators to continue to innovate are not created with a follow-on biologics pathway, we will likely see reduced private sector investment in risky early stage research activities. Academic, government and non-profit private institutions are funding the basic research activities. The venture capital industry tends to fund the promising results of these efforts in an attempt to create a human therapeutic. Once these small start-ups get the product candidate to a certain development milestone, the venture firms generally sell or partner with innovator companies which usually take the product to market and commercialization.

If a FOBS pathway provides insufficient intellectual property protection to the innovator companies, the amount they will be willing to pay for these early-stage discoveries will go down and the early stage discoveries will consequently become less attractive investments for venture capital firms. VC firms will direct their capital investment elsewhere.

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.?

Yes, such a guidance process is a necessary component of any US FOBs pathway. Guidance will ensure that FOB applicants have the information necessary to meet the requirements in the law and will ensure consistency of requirements across applications.

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?

In order for the US to maintain its position as a world leader in biotechnology research and development, the data exclusivity periods in the US should be longer than those in Europe. We believe a data exclusivity period of 14 years is necessary, as discussed above.

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?

The US would lose its position as the global leader in biotechnology research and development, which would have a negative impact on jobs in key biotechnology-intensive states such as Massachusetts and California.

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 EU regulatory pathway is a good model for the development of a US FOBs pathway. The EMEA has recognized the fundamental differences between drugs and biologics and has been focused on patient safety and rigorous scientific consideration for approval. However, as previously stated, in order for the US to maintain its position as a world leader in biotechnology research and development, the data exclusivity periods in the US should be longer than those in Europe.

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?**

We have no comment on this question, as our products have not been approved under the FFDCA nor have they been the subject of biosimilar applications in Europe.