Billy Tauzin
PRESIDENT AND
CHIEF EXECUTIVE OFFICER

PhRMA

May 2, 2008

The Honorable Frank Pallone, Jr.
Chairman, Subcommittee on Health

The Honorable Nathan Deal
Ranking Member, Subcommittee on Health

Committee on Energy and Commerce
U.S. House of Representatives
Room 316 Ford House Office Building
Washington, DC 20515-6115

Dear Representatives Pallone and Deal:

Thank you very much for your letter of April 3, 2008. You set forth a number of significant and important questions in key areas relating to the creation of any new pathway to allow for the approval of follow-on biologics (FOBs), and we are pleased to provide our responses to these questions.

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $44.5 billion in 2007 in discovering and developing new medicines. Industry-wide research and investment reached a record $58.8 billion in 2007.

PhRMA supports the development of an abbreviated pathway for the approval of FOBs that is science based, open, transparent, puts safety first, and promotes incentives for innovation. Further, PhRMA and its member companies support passage of a bill this year that meets these principles.

New biotechnology medicines often represent breakthrough advances against serious diseases such as cancer, multiple sclerosis, and rheumatoid arthritis. Research and development leading to new uses for already approved biotechnology medicines is another important source of advances which may be less familiar to the public. These new uses can include, among other things, expanding the biologic's approved uses, treating different conditions, and demonstrating improved results when used in combination with another drug ('adjunctive therapy'), or when used after the primary treatment ('adjuvant therapy'). The development of a new biologic typically spans more than a decade and costs on average more

than $1.2 billion per approved biologic. Because of the difficulty of developing new medicines and the high safety and effectiveness standards that they must meet, many biologics that enter development do not result in an FDA-approved product. In fact, even among those that enter Phase III clinical trials, thirty percent do not gain FDA approval.

We appreciate your leadership in this important policy area and the thoughtful approach in which you are soliciting views from key stakeholders on this issue. We look forward to continuing to work with you, your colleagues on the Energy & Commerce Committee, staff, and other stakeholders, as you continue consideration of this important topic.

Sincerely,

Billy Tauzin

Science/Safety

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

Immunogenicity is the ability or propensity of something to cause an immune response. While for vaccines, invoking an immune response is the desired result and how vaccination prevents infection with a bacteria or virus, immunogenicity is not desired for other biologics.

Undesired immunogenicity is a greater concern for biologics than for non-biologic, small molecule drugs because human immune systems are "trained" to see and react to large molecules - like the proteins in biologics - and not to see or react to small molecules - like most chemical drugs. Biologics frequently elicit an immune response; small molecule drugs rarely do.

The consequences of an immune response to a biologic vary greatly: there may be no noticeable clinical effect. There may be reduced efficacy because the immune response inactivates the therapeutic molecule; and reduced efficacy can pose safety risks due to the resulting disease progression. In some cases, the immune response may inactivate and destroy the naturally occurring protein as well as the therapeutic protein. This kind of autoimmunity is rare but can be life-threatening. Other severe, life-threatening immune responses can occur, though are extremely rare.

Certain quality control measures in therapeutic biologics production are known to help decrease immune responses to the product, including reducing the amount of host cell contamination and minimizing the degree to which the proteins aggregate in solution. The risks associated with an immune response to a given product may be somewhat predictable based upon clinical experience with similar products within a class. However, each FOB and innovator product will carry its own risks due to the specifics of its manufacture. Furthermore, each individual patient taking the product will have some different risks due to health status and the individuality of the immune response.

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?**

It is not possible to predict either the degree of an immune response or its consequences without data from the use of the product in patients. Because immune responses are species specific, animal studies are of limited value in predicting the type and extent of immunogenicity of a product for humans. Thorough immunogenicity assessment is an integral part of the development program and life-cycle management for any biological product and should be required for FOBs. However, the type and extent of studies, including clinical studies, that must be conducted pre- and post-approval will vary and will need to be determined case-by-case based on scientific criteria. Immunogenicity may be detected in clinical testing. However, the most serious immunological adverse events are often very rare (*e.g.*, 1 in 10,000; 1 in 100,000), and it would be unreasonable to expect to fully understand the immunogenicity of a biologic before it is approved, for innovator or follow-on products. Of course, this makes FOB post-marketing surveillance and studies essential, especially for evaluation of immunogenicity. Although

clinical experience with classes of related biologics may help FDA tailor specific studies and requirements for a given FOB[1], evaluation of immunogenicity will be necessary for approval and in the post-marketing setting.

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 has appropriately exercised its authority and should retain existing discretion to require clinical testing, including testing for immunogenicity, after manufacturing changes to a given product. Manufacturers may use comparability protocols as described in ICH Q5E[2] to show that a given product before and after a manufacturing change is comparable. Demonstration of comparability requires detailed knowledge of the entire process, and FDA's *Guidance Concerning Comparability of Human Biological Products including Therapeutic Biotechnology-Derived Proteins* requires comparisons across that process and does not rely on a comparison solely at a single step in the manufacture. A sponsor must have comprehensive knowledge of its process to establish comparability after changes, which is very challenging, even with the accumulated historical knowledge and experience with the process and the product. This is in contrast to any comparison an FOB manufacturer would make to a reference product, which would likely rely solely on comparisons made using the final finished products because the FOB manufacturer would not have knowledge of or access to the innovator manufacturing process, intermediates or the innovator drug substance before formulation.

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?**

Evidence of molecular similarity will need to be shown for all FOBs using physical and chemical analytical techniques current at the time of FOB application. Molecular similarities between two products are inherent properties of the molecules and products based on their structure, and do not provide an independent basis for determining safety and effectiveness[3] without clinical data. FOBs will be similar to the reference product, rather than identical, and thus their clinical profiles could differ from those of the reference product. Typically, innovators are required to demonstrate safety and effectiveness for each labeled indication. Safety and effectiveness for the same product may differ between indications, for example, due to route of administration or underlying disease state of the indicated condition. Safety and effectiveness for each indication of an FOB should be demonstrated unless extrapolation can be scientifically justified to FDA in a given circumstance.

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[1] However, this must be done in a manner that does not compromise proprietary information.
[2] International Conference on Harmonisation (ICH), "ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" (Nov. 2003).
[3] While the Public Health Service Act requires that FDA establish a biologic to be safe, pure and potent in order to be licensed, the Agency interprets potency to include effectiveness (see 21 Code of Federal Regulations 600.3(s) and Guidance for Industry: Providing Clinical Evidence for Effectiveness for Human Drugs and Biologics; accessed at: http://www.fda.gov/cder/guidance/1397fnl.pdf).

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 new FDA authorities for drug safety under the Food and Drug Administration Amendments Act of 2007 should extend to all drugs and biologics, including FOBs. FDA should apply the same standards for requesting post-marketing studies for FOBs that it applies to innovator products at the time of FOB approval. In some cases, this may mean that an FOB manufacturer will have different post-marketing commitments from those of the innovator product based upon the current scientific knowledge and the specifics of each product. Post-marketing commitments should be based upon what is known about the product class and about any specific safety concerns with a given product.

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?**

All biotechnology derived therapeutic proteins should have unique names so that they may be distinguished in prescribing, in dispensing, and for pharmacovigilance purposes. Therefore, an FOB should have a different name from the reference product and from other FOBs in the product class. The simplest way to achieve this is by requiring unique International Non-Proprietary Names (INNs). However, assignment of INNs is governed by the World Health Organization, outside of U.S. jurisdiction. Other mechanisms may exist under U.S. authority to assign unique names to each product, through the United States Adopted Names (USAN) Council or a requirement that each FOB bear a unique official name.

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?**

The biological activity of a protein is more difficult to characterize than that of a small molecule drug. FOBs should have the same mechanism of action as the reference product, to the degree that the mechanism of action is understood under current science, even if the mechanism of action was not understood at the time the reference product was licensed.

The mechanism of action of the protein is a direct result of its molecular structure. Two proteins with similar structures should, as a general matter, have the same mechanism of action. Proposed FOB approval pathways are based on the premise that the FOB is similar to the reference product. Differences between the FOB and the reference product could result in

different mechanisms of action, in which case, the FOB pathway would not be appropriate and the product should be evaluated under a full BLA submission.

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?

Biologics are heterogeneous because the living systems that produce them are heterogeneous with processes that do not operate at 100% fidelity, and the degree of variability differs by product. Different processes will produce different types and degrees of heterogeneity and impurities. Individual manufacturers control and understand the heterogeneity of the final product through each step in their process, controlling process and product impurities. Each manufacturer must link the heterogeneity of the product, as understood through intimate process knowledge and control, to the clinical data demonstrating the safety and effectiveness of the product. The release specifications (*i.e.*, a list of qualified assays and the acceptable value ranges for these assays) for a given final product describe the final product but reflect the many in-process controls that are not a part of the specifications and are linked to the clinical data. It is inappropriate to use specifications for one product and its process for another unrelated process and product.[4] Therefore, FOB manufacturers must establish their own set of specifications that reflect their own process variability and their knowledge and control of that process.

Differences in product quality as a result of manufacturing changes are assessed and controlled through comparability protocols. Manufacturers may use comparability protocols as described in ICH Q5E[5] and *FDA's Guidance Concerning Comparability of Human Biological Products, including Therapeutic Biotechnology-Derived Proteins* to show that a given product before and after a manufacturing change is comparable. Demonstration of comparability requires detailed knowledge of the entire process and comparisons across that process and does not rely on a comparison at a single step in the manufacture. A sponsor must have comprehensive knowledge of its process to establish comparability after changes, which is very challenging, even with the accumulated historical knowledge and experience with the process and the product. This is in contrast to any comparison an FOB manufacturer would make to a reference product, which would likely rely solely on comparisons made using the final finished products because the FOB manufacturer would not have knowledge of or access to the innovator manufacturing process, intermediates or the innovator drug substance before formulation. If an innovator's manufacturing changes are substantial enough, FDA will require clinical studies for safety and effectiveness. Differences in manufacturing between an FOB and reference product are likely to be of sufficient magnitude that they would warrant clinical studies for safety and effectiveness even if these changes were made by a single manufacturer.

[4] *See* International Conference on Harmonisation, "ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" (Aug. 1999).
[5] International Conference on Harmonisation (ICH), "ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" (Nov. 2003).

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?**

Fundamentally, an FOB would be similar to, and not the same as, the reference product. There is no scientific justification for basing approval of a biological product solely on clinical data derived from a different biological product made by different manufacturing processes. Therefore, clinical trials should be required to demonstrate the safety and effectiveness of all FOBs. These trials may be less extensive or different from those to approve the reference product, based upon the current science and the accumulated clinical experience with the reference product. FDA should have the discretion to establish by guidance the type and extent of clinical trial data necessary to support FOB applications in a given product class, including approval and post-approval expectations.

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

FDA officials have stated their view of prior approvals under section 505 and the data required for those products.[6]

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?**

PhRMA does not have information on the marketplace experience of specific products.

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?**

[6] Woodcock, J. et al. "The FDA's assessment of a follow-on protein products: a historical perspective," *Nature Reviews Drug Discovery* (6):437-42 (June 2007).

A single approval pathway should be created for follow-on versions of therapeutic protein products whether approved under the FFDCA or licensed under the Public Health Service Act (PHSA). The evaluation of FOBs requires an approval pathway tailored to the distinct challenges and concerns associated with biological products. These include risks posed by undesirable immunogenicity, extreme sensitivity to manufacturing processes, inherent heterogeneity among biological substances, and difficulties in characterization. The benefits of FDA developing product-class specific guidance for FOBs through a transparent stakeholder process, and the medical and scientific considerations that must be taken into account during review of an FOB application, are the same regardless of the statute under which the reference product was approved. A single regulatory pathway will enable FDA to develop uniform and comprehensive regulatory frameworks, scientific standards, and administrative processes for the review and approval of all FOBs, and will have the further benefit of not creating artificial distinctions between products and generating unjustified complexity and confusion.

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?**

The FFDCA gives FDA discretion to decide whether clinical data are needed to support a manufacturing change for an approved innovator biological product, and this is grounded in sound science. With innovator products, FDA can assess a change in the context of the full data package submitted with the product's BLA, including detailed trade secret information about the active substance and final product, the manufacturing processes, and previous comparability testing for the product. FDA has access to information obtained from the innovator manufacturer's many years of experience with the approved product. The agency is therefore in a position to make an informed assessment of the risks associated with, and the data needed to support, a manufacturing change. In contrast, in the context of an FOB application, the FOB applicant does not have access to this critical information about the reference product, and FDA cannot legitimately use any to the benefit of the FOB applicant.

Experience has demonstrated that even seemingly minor manufacturing differences can have profoundly negative consequences for patient care. Accordingly, FDA regularly has required clinical data to support the comparability of an approved product before and after a change in its manufacturing processes, starting materials, or facilities. Validation that such changes have little or no impact on the innovator product is challenging and requires a comprehensive knowledge of the entire manufacturing process and product characteristics, a knowledge that the FOB applicant would not possess.

Unlike the changes made to the manufacture of approved biological products, the number and types of changes involved in the manufacture of an FOB effectively amount to use of an entirely novel manufacturing process and new cell line. FOB manufacturing is conducted by a different firm, in different facilities, using different equipment, with different sources for starting materials, and under different specifications for the active substance and finished product than those used to manufacture the innovator product. Current laboratory testing methods are

inadequate to detect all of the differences between an FOB and a reference product that can adversely affect patient health. Frequently with biological products, only clinical data can provide vital information about the effect changes will have on a product's safety and effectiveness profiles. It is highly doubtful that an FOB applicant could justify the extensive differences entailed in the manufacture of the FOB without clinical data validating those deviations from the manufacture of the reference product.

FOB legislation in the United States should therefore establish the submission of supportive clinical data as a minimum requirement for FOB approval. FDA should be permitted to exercise discretion concerning whether and what additional information is needed beyond core, statutorily-prescribed application requirements.

3. **What FDA office should review FOBs?**

The FDA division that reviews a proposed FOB should be the division that reviewed the application for the designated reference product. The division responsible for reviewing the reference product should have expertise in the relevant product class and therapeutic area and is best suited to leverage existing resources to conduct the review. Legislation should require FDA to establish procedures designed to ensure that the division reviewing an FOB application does not review or rely on the reference product sponsor's trade secrets (*e.g.,* its manufacturing process) during such review.

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?**

FOBs and their reference products will not be the same. However, certain minimum standards for physical similarity must be established. These should require that the FOB applicant fully characterize its own product, compare it to the reference product, and characterize any detected differences. FOBs should also be required to have the same mechanism of action as the reference product, to the degree that the mechanism of action is understood under current science, even if the mechanism of action was not understood at the time the reference product was licensed. Notwithstanding any structural similarities, the FOB applicant should demonstrate similar safety and effectiveness through pre-clinical and clinical studies, including comparative clinical studies with the reference product.

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?**

We strongly support the use of open, transparent, and public processes to develop regulations and guidance to implement a new regulatory pathway for the approval of FOBs. FDA's careful consideration of public comments is critical to promoting patient safety and patient confidence in new medicines. The processes and standards that FDA develops should reflect the agency's best judgments about currently available science and medicine. The agency can best achieve optimal results if its regulations and guidances are informed by the perspectives and experience of interested stakeholders, including innovator manufacturers, FOB manufacturers, physicians, patients, and academic experts.

Requiring FDA to flesh out the regulatory scheme governing FOB approval through open and public processes would be consistent with the approach taken in Europe. A hallmark of the European process for approving biosimilar products has been the transparent process through which the European Medicines Agency (EMEA) has developed the regulatory scheme for biosimilar approval. The EMEA has issued concept papers and draft guidances and held public scientific workshops. It has issued general principles and an over-arching framework for approval of biosimilars, as well as product-class specific guidances that set forth product requirements in greater detail. At each stage, the EMEA has sought and received extensive public comments.

Although it will take time for FDA to develop and implement any regulatory framework for FOB approval, product-class specific proceedings could be initiated a reasonable period after innovator products are approved. This would provide the FDA with sufficient time to receive and assess comments before a reasonable period of data exclusivity expires, but would still allow regulations and guidance to benefit from sufficient experience with the reference product class to inform the requirements for an abbreviated approval. Estimates vary as to the length of time needed to develop regulations and guidance for FOBs. Duke University economist Henry Grabowski concluded that "several years are likely to elapse before a follow-on product is approved and launched in the United States."[7]

However, it is anticipated that over time, regulations and guidances as well as the transparent processes for developing them, may ultimately conserve applicant and FDA resources and lead to an increase in the speed with which FOB applications are reviewed and approved. If FDA issues guidance that makes its expectations and approval considerations explicit and clear, FOB manufacturers may be able to concentrate their resources more effectively and may be more likely to submit applications acceptable for review. FDA can review applications more efficiently if it receives applications ready for review and encounters fewer delay-causing issues during the review and can therefore be more consistent in its review of applications within a given product class. This could help reduce risk and uncertainty for future FOB applicants. As the Secretary of Health and Human Services has stated, a requirement that FDA issue product-specific guidance before acting on FOB applications will help "ensure the agency has optimum information regarding safety and efficacy considerations for follow-on products; enhance

[7] Statement of Henry G. Grabowski, Ph.D., Duke University, before the H. Comm. on Oversight and Government Reform 8-9 (Mar. 26, 2007), *available at* http://oversight.house.gov/story.asp?ID=1223.

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."[8]

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?**

Because an FOB application will rely in part on innovator safety and effectiveness data, the quantity of data needed to support an FOB application may be less than what is needed to support an innovator Biologics License Application (BLA). Even so, the full range of scientific, medical, and statistical expertise that must be brought to bear to review FOB applications will be comparable to what is currently needed for FDA's review of innovator biological products. Thus, the funding needed to support an FOB approval program will undoubtedly be substantial. FOB applicants should be required to pay commensurate user fees as NDA and BLA applicants to supplement FDA appropriations.

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 permit a determination of interchangeability for biologic products produced by different manufacturers. Biologics made through different processes, which will include different cell lines, different master cell banks, different fermentation, different purification and different formulation will be different products. There is currently no scientific basis for interchangeability of two different biological products, and no scientific consensus for how an adequate scientific model could be established to determine it. Interchangeability of generic small molecule drugs is based on the premise that the active ingredients are the same; this is not the case for FOBs and their reference products.

While FDA is confident in the ability to approve safe and effective FOBs, it also has stated that the ability to determine interchangeability for FOBs, in particular for more complex proteins, may be limited.[9]

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[8] Letter from Michael O. Leavitt, Secretary of Health and Human Services, to Sen. Edward M. Kennedy 3 (June 26, 2007).

[9] Examining Safe and Affordable Generic Biotech Drugs: Hearing before the House Committee on Oversight and Government Reform, 110th Cong. (March 26, 2007) (statement of Janet Woodcock, Deputy Commissioner and Chief Medical Officer, U.S. Food and Drug Administration) at pg 9, also available at (http://oversight.house.gov/story.asp?ID=1223).

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

The FOB applicant must complete a rigorous analytical, pre-clinical and clinical program to demonstrate similarity to the reference product, to warrant approval under an abbreviated pathway. However, the type and scope of testing that would be needed to demonstrate interchangeability of two different biologics is unknown because there is no scientific rationale for interchangeability of different substances at present and no consensus within the scientific community regarding this concept. Therapeutic equivalence of generic small molecule drugs is based on the premise that the active ingredients are the same; this is simply not the case for FOBs.

Due to the risks posed by substituting one biological product for another, including the potential for serious adverse events, such as immunogenicity, it is critical that FDA be informed by well-developed science and public comments before making any interchangeability determinations.

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.**

Current science does not permit a determination of interchangeability for biologic products produced by different manufacturers. Biologics made through different processes, which will include different cell lines, different master cell banks, different fermentation, different purification and different formulations, will be different products. If and when the science permits, FDA should establish product-class specific guidances on interchangeability at their discretion, after expert consultations and with appropriate public comment periods.

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?**

Current science does not permit a determination of interchangeability for biologic products produced by different manufacturers. Biologics made through different processes, which will include different cell lines, different master cell banks, different fermentation, different purification and different formulation will be different products. If and when the science permits, FDA should establish product-class specific guidances on interchangeability at their discretion, after expert consultations and with appropriate public comment periods.

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?**

Current science does not permit a determination of interchangeability for biologic products produced by different manufacturers. Biologics made through different processes, which will

include different cell lines, different master cell banks, different fermentation, different purification and different formulations, will be different products. There is currently no scientific basis for interchangeability of two different biological products, and no scientific consensus for how an adequate scientific model could be established to determine it.

In the absence of a clear scientific basis for establishing interchangeability between products that are similar, the risk to patients of making such determination is unacceptable. Different biological products affect individuals differently. Using one biologic product in place of another creates significant concerns about the potential for immunogenicity and serious adverse events. FDA would not make such determination until and unless there were a scientific basis and the risk to patients would be minimized. Thus, if the time comes that FDA makes a determination of interchangeability, it should be done in a way that makes physicians and patients feel comfortable.

It is impossible to assess at this time how interchangeability might impact patient access. There are several factors that would potentially influence the acceptability of FOBs among payers, patients, physicians, and pharmacists and hence patient access would include how and by whom interchangeability is determined (*e.g.*, process and criteria). First, as a threshold matter, the acceptability of FOBs among patients and physicians likely will be significantly affected by how interchangeability is determined (*e.g.*, process and criteria) and patients' and physicians' experiences with adverse events, allergic reactions, etc. Second, access will be affected by how insurers elect to cover both the innovator biologic and any FOB. It would be speculative to predict insurers' coverage strategies (which may or may not be affected by how interchangeability would be determined), including the extent of patient cost-sharing for innovator and follow-on molecules, how that would vary from current coverage strategies, and the possibility of differential effects on patients currently receiving a biologic versus those newly starting. Third, questions of access also should consider access to a continuing stream of newly developed biologics that exploit the growing understanding of the biological basis of disease and newly-established indications for biologics. A pathway for FOBs may support or hinder such continued development of new treatments, depending on its specific features.

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

There are substantial uncertainties regarding how the potential market for FOBs would evolve, including whether interchangeability can be scientifically established for particular types of large molecules. As mentioned in the response to Question 5, Interchangeability, this in turn would affect the degree of confidence and acceptance of FOBs among physicians, patients, and payers. It also would be speculative to project how insurers will choose to cover innovator and FOBs, including the extent of patient cost-sharing for innovator and FOBs, how that would vary from current coverage strategies, and the possibility of differential effects on patients currently receiving a biologic versus those newly-starting. As a result of these and other uncertainties, we are unable to project how the market for biologics ultimately may be affected in terms of competition, costs, and reimbursement for innovator and FOBs.

When considering competition in the marketplace, it also is important to consider competition among innovator biologics. As Calfee (2008)[10] shows, competition is increasingly present in many therapeutic categories and may involve competition on price as well clinical effects. Since this competition is an important source of medical advances, the effect of a follow-on pathway on brand-to-brand competition, including both its economic and clinical aspects, also should be considered when assessing issues of competition in the biologics market.

Patents

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

The importance of patents to continued innovation has been demonstrated in several economic analyses.[11] Given the research-intensive nature of this sector, patents are more critical to the continued viability of the biopharmaceutical industry than for any other sector of the economy (see, for example, Mansfield, 1986).[12] As reported in one study, 65 percent of innovations in the pharmaceutical industry would not have been brought to market without patents (Mansfield 1986).[13] "[I]n addition to motivating innovation, patents also serve a society purpose of encouraging disclosure and thus providing a means for the wide diffusion of technological information," according to Barfield and Calfee (2007).[14] In the pharmaceutical industry, short and possibly declining market exclusivity periods present increasing challenges.[15] In fact, only two out of ten pharmaceuticals now earn a return sufficient to cover the average cost of the research and development needed to bring a drug to market.[16] As a result, any action that further impairs patent protection for innovative pharmaceutical products could substantially reduce the number of new medicines that come to market.

Despite the particular importance of intellectual property incentives for biopharmaceuticals, analyses of the effective patent life - defined as the remaining patent time at a drug's launch date - for innovator pharmaceutical companies show that it is far less than the actual patent life for

[10] Calfee, J, "White Paper on Pharmaceutical Market Competition Issues" (Apr. 2008).
[11] *See, e.g.*, Mansfield, E, "Patents and Innovation: An Empirical Study," *Managerial Science* 173-81 (2:1986); Scherer, FM, "The Political Economy of Patent Reform in the U.S.," Harvard University Working Paper No. RWP07-042 (2007), *available at* www.researchinnovation.org/scherer/patpolic.pdf.
[12] Mansfield, E, "Patents and Innovation: An Empirical Study," *Managerial Science* 173-81 (2:1986). In: Barfield, C, and Calfee, J. "Biotechnology and the Patent System: Balancing Innovation and Property Rights." Washington, DC: American Enterprise Institute, (2007:27).
[13] Mansfield, E, "Patents and Innovation: An Empirical Study," *Managerial Science* 173-81 (2:1986), In: Barfield, C, and Calfee, J. "Biotechnology and the Patent System: Balancing Innovation and Property Rights." Washington, DC: American Enterprise Institute, (2007:27).
[14] Barfield, C, and Calfee, J, "Biotechnology and the Patent System: Balancing Innovation and Property Rights," American Enterprise Institute, (2007:29).
[15] DiMasi, JA & Grabowski, HG, "Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D" (June 25, 2004), *available at* www.who.int/intellectualproperty/news/en/Submission3.pdf.
[16] Vernon, J, Golec, R & DiMasi, J, "Drug Development Costs When Financial Risk is Measured Using the FAMA-French Three Factor Model," unpublished working paper (2008).

innovators in other industries. DiMasi et al. (2003)[17] found that because innovators apply for patents at the beginning of the clinical development process, much of the nominal 20-year patent term is lost by drugs by the time of FDA approval. As discussed by Calfee and Barfield (2007), "a decade or more can be occupied in testing, in constructing and validating manufacturing facilities, and in otherwise dealing with FDA and other regulatory oversight and review."[18]

Recent research by Grabowski and Kyle (2007) calculates the market exclusivity period for pharmaceuticals, which they define as the amount of time a brand pharmaceutical is on the market before generic entry.[19] This average was only 11.2 years for medicines first experiencing generic entry in the period 2002-2005 (and even shorter for some brand drugs with larger sales). This shortened period of market exclusivity is the case notwithstanding the patent term restoration provisions of Hatch-Waxman. As noted by the authors, the actual terms will vary by specific product, and further research is needed using more recent data. Grabowski and Kyle found that the number of patent challenges occurring early in a pharmaceutical's life cycle (Paragraph IV filings[20]) has grown dramatically in recent years. They conclude that these trends have and will continue to contribute to even shorter market exclusivity periods in the future. They also found that generic firms are, increasingly "prospecting", challenging patents of major products early in the product's life cycle even if there is a low probability of the patent being found invalid, unenforceable, or not infringed.

Patent-term restoration provides partial compensation to the patent term for some of the effective patent life lost due to the clinical development and regulatory review processes. However, it has substantial limitations as an incentive. First, restoration can be applied to only one patent per product, and it must be a patent existing and in force prior to the time of approval of the product. Second, restoration provides only partial compensation because (1) none of the pre-clinical period is considered, (2) one-half of the clinical research period is not considered in the calculation, (3) the total restoration period cannot exceed five years, and (4) the total effective patent life including the restored period cannot be more than 14 years. Many patents do not reach the 14-year cap even with patent term restoration, and thus the product does not get the benefit of 14 years of effective patent life from the patent. The list on the PTO website of patent terms restored under 35 U.S.C. § 156 illustrates that, even with the restored term, the time from approval to expiration of the restored patent for most products was less than 14 years.

It should also be recognized that brand medicines face increasingly rapid competition from other brand medicines in their therapeutic class. DiMasi and Paquette (2004)[21] report that the average

[17] DiMasi, JA, Hansen R, and Grabowski, H. The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics* 141-85 (22:2003).
[18] Barfield, C, and Calfee, J, "Biotechnology and the Patent System: Balancing Innovation and Property Rights," American Enterprise Institute, (2007:28).
[19] Grabowski, HG, and Kyle, M, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 491 28:2007).
[20] In filing an Abbreviated New Drug Application, a generic manufacturer must make one of four patent certifications with respect to each patent listed for the reference product. Paragraph IV refers to the certification that the generic product would not infringe the patent when marketed or that the patent is not valid. If the generic applicant makes a Paragraph IV certification, the innovator company may bring a patent infringement action.
[21] DiMasi, JA, and Paquette, C, "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and Timing of Development," *Pharmacoeconomics* 1-14 (22 Supp 2:2004).

period of time elapsing between a first-in-class drug entering the market and a second brand entering that class declined from 10.2 years in the 1970s to 1.2 years by the late 1990s. Moreover, later entrants to a class generate price competition. DiMasi and Paquette (2004)[22] found that "the average percentage change was a 26% discount relative to the price leader and a 14% discount relative to the class average."

The potentially negative impact of declining effective patent life and market exclusivity periods for future innovation - given the high costs, lengthy timeframe, and uncertainty involved in biologics research and development - could potentially be offset for biologics by coupling patent protection with a minimum data exclusivity period of at least 14 years before approval of an FOB. Once a pathway is established, it will be important to ensure that the patent-term restoration provisions do not provide weaker incentives than in the drug context.

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?**

Patent term restoration and data exclusivity are both necessary incentives for biologics innovation. Data exclusivity associated with a follow-on biologics pathway should be at least 14 years, with additional exclusivity available for post-approval indications.

Patents and data exclusivity are both incentives for investment in innovation. They work in a complementary fashion. Patents reward an invention by providing the innovator with the right to prevent anyone else from making, using or selling the patented invention for a defined period of time. Data exclusivity recognizes the large-scale investment required to develop safety and effectiveness data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and effectiveness of its product. Neither patents nor data exclusivity bar other innovators with competing, non-infringing drugs from the market.

As the Hatch-Waxman compromise for drugs reflects, patent protection is necessary but not alone sufficient to provide adequate incentives for medical innovation. Some of the patent life necessarily is lost during the time consumed by the extensive development and FDA approval process that is required to bring a new medicine to market, and patent term restoration provides only partial compensation for this lost time. Further, in the case of biologics, a product patent may provide insufficient protection if an FOB applicant can circumvent the patent under the similarity standard for FOB approval. Moreover, patents nearly always have a measure of uncertainty, but investments in the testing and clinical trials needed to obtain FDA approval must be made long before an innovator knows whether a patent may someday be successfully challenged. Data exclusivity provides a measure of certainty, allowing investments in clinical trials to be supported. Data exclusivity also provides an incentive for continued research leading to new indications post-approval and after patents have expired. Because patents are filed relatively early in the clinical development process, when a drug is launched it may have a

[22] DiMasi, JA, and Paquette, C, "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and Timing of Development," *Pharmacoeconomics* 1-14 (22 Supp 2:2004:2).

decade or less of effective patent life remaining. Data exclusivity, which is independent of patents, runs from the time of FDA approval. Thus, patent terms and data exclusivity often run concurrently.

The uncertainty of patent protection, which emphasizes the need for data exclusivity, is evident in the research of Grabowski and Kyle (2007).[23] They found that the number of patent lawsuits associated with Paragraph IV filings has grown in recent years and that these legal challenges are occurring much earlier in the drug's lifecycle. Grabowski and Kyle (2007) conclude that these trends are shortening the average time that innovators have to attempt to recoup their research and development investment. According to Grabowski (2007), "[m]ost of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an ANDA filing with a paragraph IV certification."[24] Grabowski (2007) concludes that these challenges and the accompanying "uncertainty adversely impacts biopharmaceutical research and development resulting in firms abandoning research and development projects on future drug candidates with uncertain patent prospects. Early patent challenges also can have a chilling effect on the development of new indications and formulations, given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval."[25]

Duke University economist Henry Grabowski has calculated the appropriate period of data exclusivity for biologics as being 12.9 to 16.2 years, based on the estimated period of time it takes a portfolio of biologics marketed by a mature company to earn back the average cost of R&D needed to bring a new biologic to market.[26] We believe this and other research justifies a period of at least 14 years of data exclusivity for biologics. Additional exclusivity should be available for post-approval indications, in light of the central importance of post-approval research to achieving medical progress and the investment needed to support the clinical trials required to obtain an FDA-approved new indication.

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?**

Once a regulatory approval pathway has been enacted for FOBs, innovators of these products may receive less protection from their patents than traditional small molecule innovators receive as a result of the standard of approval envisioned in an FOB pathway. The cornerstone for approval of a generic drug product is the requirement that it be the "same as" the reference drug. A generic drug approved under section 505(j) is likely to infringe the reference drug's product

[23] Grabowski, HG & Kyle, M, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 492 (2007).
[24] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[25] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[26] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

patent because the generic drug's active ingredient is - by statutory necessity - the same as the reference product's active ingredient. The sameness standard for ANDA approval, although grounded in public health considerations, therefore has the added effect of preserving the protection offered by innovator patents. A regulatory approval process for FOBs would be based on similarity, rather than sameness, which would introduce greater uncertainty about whether a particular innovator product patent can be enforced against an FOB.

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 patent litigation procedure could be drafted in a variety of ways. Any such procedure, however, needs to create a mechanism in the biologics licensing statute administered by FDA (*i.e.*, title 42) for:

- the FOB applicant and patent holders to have sufficient opportunity - before marketing by the FOB applicant - to identify relevant patents (*i.e.*, those that are potentially infringed by an FOB application), including by providing patent holders with confidential access to the application and a detailed explanation of the FOB's manufacturing processes;

- prompt resolution of patent disputes through adjudication prior to an FOB's entry on the market (including by enabling patent holders to be notified when an FOB applicant intends to launch its product and to seek injunctive relief);

- encouraging resolution of patent disputes before approval of the FOB upon expiration of the innovator product's data exclusivity period;

- keeping FOBs that infringe a patent off the market (by preventing final FDA approval until patent expiry); and

- enforcing the requirements set forth in the procedure.

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?**

Any workable approval pathway for FOBs must permit both third party patent holders and product sponsors to have a meaningful ability and opportunity to protect their intellectual property interests.

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?**

Any workable approval pathway for FOBs must provide each FOB applicant with a way to determine or be notified of the patents it risks infringing and to be able to resolve patent disputes prior to the expiration of applicable data exclusivity. There may be several ways to achieve the notification objective. For example, legislation could require that notice be given (directly to specified parties and through publication) of an applicant's submission of an FOB application to FDA, and that parties with relevant patent interests notify the FOB applicant of those patents. A process incorporating patent listing and notification provisions is another potential approach.

Regardless of the particular method established for identifying relevant patents, the method must take into account the unique features of biological products. For example, given the significance of manufacturing processes in the development of safe and effective biological products, any FOB legislation must enable FOB applicants and innovators to identify relevant process patents as well as product patents. It must also account for the fact that the list of relevant patents may evolve over time as the processes involved in a product's manufacture (by an innovator or FOB applicant) change or a manufacturer's knowledge about a biological product further develops.

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?**

Patent term restoration and data exclusivity are both necessary incentives for biologics innovation. Data exclusivity associated with a follow-on biologics pathway should be at least 14 years, with additional exclusivity available for post-approval indications.

Patents and data exclusivity are both incentives for investment in innovation. They work in a complementary fashion. Patents reward an invention by providing the innovator with the right to prevent anyone else from making, using or selling the patented invention for a defined period of time. Data exclusivity recognizes the large-scale investment required to develop safety and effectiveness data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and effectiveness of its product.

The question refers to "exclusive marketing" which differs from data exclusivity. Data exclusivity does not prevent an applicant from submitting an application and obtaining approval based solely on its own data. Market exclusivity would prevent approval of an application within the exclusivity period even if the applicant used its own data. Neither patents nor data exclusivity bar other innovators with competing, non-infringing drugs from the market.

As the Hatch-Waxman compromise for drugs reflects, patent protection is necessary but not alone sufficient to provide adequate incentives for medical innovation. Some of the patent life necessarily is lost during the time consumed by the extensive development and FDA approval process that is required to bring a new medicine to market, and patent term restoration provides

only partial compensation for this lost time. Further, in the case of biologics, a product patent may provide insufficient protection if an FOB applicant can circumvent the patent under the similarity standard for FOB approval. Moreover, patents nearly always have a measure of uncertainty, but investments in the testing and clinical trials needed to obtain FDA approval must be made long before an innovator knows whether a patent may someday be successfully challenged. Data exclusivity provides a measure of certainty, allowing investments in clinical trials to be supported. Data exclusivity also provides an incentive for continued research leading to new indications post-approval and after patents have expired.

The uncertainty of patent protection, which emphasizes the need for data exclusivity, is evident in the research of Grabowski and Kyle (2007).[27] They found that the number of patent lawsuits associated with Paragraph IV filings has grown in recent years and that these legal challenges are occurring much earlier in the drug's lifecycle. Grabowski and Kyle (2007) conclude that these trends are shortening the average time that innovators have to attempt to recoup their research and development investment. According to Grabowski (2007), "[m]ost of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an ANDA filing with a paragraph IV certification."[28] Grabowski (2007) concludes that these challenges and the accompanying "uncertainty adversely impacts biopharmaceutical research and development resulting in firms abandoning research and development projects on future drug candidates with uncertain patent prospects. Early patent challenges also can have a chilling effect on the development of new indications and formulations, given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval."[29]

Duke University economist Henry Grabowski has calculated the appropriate period of data exclusivity for biologics as being 12.9 to 16.2 years, based on the estimated period of time it takes a portfolio of biologics marketed by a mature company to earn back the average cost of R&D needed to bring a new biologic to market.[30] We believe this and other research justifies a period of at least 14 years of data exclusivity for biologics. Additional exclusivity should be available for post-approval indications, in light of the central importance of post-approval research to achieving medical progress and the investment needed to support the clinical trials required to obtain an FDA-approved new indication.

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?**

[27] Grabowski, HG & Kyle, M, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 492 (2007).
[28] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[29] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[30] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

As discussed in the previous response, the economic analysis by Grabowski (2007)[31] provides a carefully reasoned assessment of the average period of data exclusivity necessary to encourage the development of new medicines without unduly delaying the entry of FOBs. The break-even analysis for a representative portfolio of biologics provides support for a substantial data exclusivity period of between 12.9 and 16.2 years based on differing costs of capital. While conceptual models of optimal exclusivity periods have been developed by other economists,[32] such modeling efforts have not resulted in a specific value for the data exclusivity period. The Biotechnology Industry Organization (BIO) reviewed available data and research including the analysis by Grabowski and supports a minimum of 14 years of data exclusivity "to ensure that those companies with approved products are able to receive an appropriate return on their investment, and that the development stage companies can continue to finance their operations through accessing the venture and equity markets with the opportunity for an appropriate return in the future."[33]

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

A base data exclusivity period of at least 14 years should be provided to innovator biologics, and an additional period of exclusivity should be provided for new indications. These new indications can include, among other things, expanding the biologic's approved uses, treating different conditions or different patient populations, or demonstrating improved results when used in combination with another medicine. Further, second-generation biologics, which require new, full BLAs, should receive 14 years of data exclusivity because they are new products. Second-generation biologics are biological products that have new active substances with different molecular structures, physical properties and clinical features from the first-generation biologic. Approvals of such products are based on substantial data, and can provide substantial therapeutic benefits and improved patient outcomes. Ultimately, the marketplace should determine the value and extent to which second-generation biologics provide a clinically meaningful advantage over an FOB for a first-generation biologic. In this context, second generation biologicals are new molecules, not new formulations or new combinations of existing molecules.

In a recent study, 47 percent of biologics regulated by FDA's Center for Drug Evaluation and Research were found to have at least one new FDA-approved indication after the initial approval[34]. Moreover, in 2007 biologics that have been on the market for more than 7 years continue to generate new indications, and trials for new indications are ongoing for biologics approved 10 or more years ago. This understates the R&D related to new indications as more recently approved biologics may not yet have initiated research into new indications or may

[31] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[32] *See, e.g.*, Nordhaus, W, "Invention, Growth and Welfare: A Theoretical Treatment of Technological Change" (MIT Press 1969).
[33] Biotechnology Industry Organization, "A Follow-On Biologics Regime Without Strong Data Exclusivity Will Stifle The Development Of New Medicines," (p.1) *available at* http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf.
[34] Boston Consulting Group, "How Biological Drugs Continue to be Developed Long After Their First Approval: Quantitative Study of New Indications Approved in the U.S." (2007).

currently have clinical or other research under way, which may lead to new or expanded indications.

Citing the record of advances achieved by post-approval research on biologics, Calfee has written that "medicine today is actually in a new golden era of innovation."[35] Calfee concludes that, "The dominant role of post-approval research extends to many other drugs used as what are called 'targeted therapies'….Some of these targeted therapies find value in treating a completely different illness. More successes are, no doubt, on the way."[36] The potential significance of post-approval research to future medical advances is evident in the following illustrative examples[37]:

- A biologic originally approved as a first-line treatment for patients with metastatic carcinoma of the colon and rectum in combination with chemotherapy was later approved as part of a combination therapy to treat non-small cell lung cancer as well as approved as an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer. According to the manufacturer's website, there are more than 20 clinical trials under development exploring its potential against more than 10 different cancers.

- Another biologic, first approved to treat moderate to severe rheumatoid arthritis, has since received approval for more than 10 new indications ranging from psoriatic arthritis and moderate to severe juvenile rheumatoid arthritis.

- A biologic, first approved to treat hairy cell leukemia, has received approval as a treatment for hepatitis B in adults and pediatric populations as well as for treatment of select patients with AIDS-related Kaposi's sarcoma (for more information, please see PhRMA 2007[38]).

The research needed to gain FDA approval for a new indication includes clinical trials to determine the treatment's safety and effectiveness for the particular indication—just as such trials are required for initial approval. When clinical trials are completed, FDA reviews the application and determines whether to approve the new use, along with the specific parameters of and information about that use to be included in the biologic's labeling. Boston Consulting Group estimates that it takes three to six years to achieve FDA approval of a new indication.[39] There also are no guarantees that a new indication will be approved. As with trials for initial approval of a new biologic, trials to support a new indication may fail to achieve the desired

[35] Calfee, J. The Golden Age of Innovation. *The American* (Mar./Apr. 2007), *available at* http://www.american.com/archive/2007/march-april-magazine-contents *available at* http://www.innovation.org/index.cfm/NewsCenter/FeaturedStudies?NID=41
[36] Calfee, J, "The Golden Age of Innovation," *The American* (Mar./Apr. 2007), *available at* http://www.american.com/archive/2007/march-april-magazine-contents.
[37] PhRMA. "Post Approval Research on Biotech Medicines Leads to Key Medical Advances." (Oct 2007) *available at* http://www.innovation.org/index.cfm/NewsCenter/FeaturedStudies?NID=41.
[38] PhRMA. "Post Approval Research on Biotech Medicines Leads to Key Medical Advances." (Oct 2007) *available at* http://www.innovation.org/index.cfm/NewsCenter/FeaturedStudies?NID=41.
[39] Boston Consulting Group, "Continued Development of Approved Biological Drugs: A Quantitative Study of Additional Indications Approved Postlaunch in the United States" (2007).

result, and/or a new indication that is researched and tested may not be approved by FDA. For all these reasons and because post-approval research must have an opportunity to earn a return in order to be viable, a significant period of data exclusivity for new indications (in addition to the data exclusivity awarded to a product upon its initial approval by FDA) is a key incentive for encouraging continuation of this vitally important form of advancing medical care.

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

Patent term restoration and data exclusivity are both necessary incentives for biologics innovation. Data exclusivity associated with a follow-on biologics pathway should be at least 14 years, with additional exclusivity available for post-approval indications.

Patents and data exclusivity are both incentives for investment in innovation. They work in a complementary fashion. Patents reward an invention by providing the innovator with the right to prevent anyone else from making, using or selling the patented invention for a defined period of time. Data exclusivity recognizes the large-scale investment required to develop safety and effectiveness data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and effectiveness of its product. Neither patents nor data exclusivity bar other innovators with competing, non-infringing drugs from the market.

As the Hatch-Waxman compromise for drugs reflects, patent protection is necessary but not alone sufficient to provide adequate incentives for medical innovation. Some of the patent life necessarily is lost during the time consumed by the extensive development and FDA approval process that is required to bring a new medicine to market, and patent term restoration provides only partial compensation for this lost time. Further, in the case of biologics, a product patent may provide insufficient protection if an FOB applicant can circumvent the patent under the similarity standard for FOB approval. Moreover, patents nearly always have a measure of uncertainty, but investments in the testing and clinical trials needed to obtain FDA approval must be made long before an innovator knows whether a patent may someday be successfully challenged. Data exclusivity provides a measure of certainty, allowing investments in clinical trials to be supported. Data exclusivity also provides an incentive for continued research leading to new indications post-approval and after patents have expired. Because patents are filed relatively early in the clinical development process, when a drug is launched it may have a decade or less of effective patent life remaining. Data exclusivity, which is independent of patents, runs from the time of FDA approval. Thus, patent terms and data exclusivity often run concurrently.

The uncertainty of patent protection, which emphasizes the need for data exclusivity, is evident in the research of Grabowski and Kyle (2007).[40] They found that the number of patent lawsuits associated with Paragraph IV filings has grown in recent years and that these legal challenges are occurring much earlier in the drug's lifecycle. Grabowski and Kyle (2007) conclude that these trends are shortening the average time that innovators have to attempt to recoup their research

[40] Grabowski, HG & Kyle, M, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 492 (2007).

and development investment. According to Grabowski (2007), "[m]ost of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an ANDA filing with a paragraph IV certification."[41] Grabowski (2007) concludes that these challenges and the accompanying "uncertainty adversely impacts biopharmaceutical research and development resulting in firms abandoning research and development projects on future drug candidates with uncertain patent prospects. Early patent challenges also can have a chilling effect on the development of new indications and formulations, given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval."[42]

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

As stated in our previous responses in this section, based on the economic analysis conducted by Grabowski (2007),[44] a minimum base period of 14 years is needed to balance the incentives needed to develop new medicines with the interest in additional price competition through the entry of FOBs. In fact, the market dynamics for small molecule drugs have changed dramatically since the passage of the Hatch-Waxman Act such that even the data exclusivity period for small molecule drugs is insufficient[45] [46]

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

Due to the research intensive nature of the biologics sector, both patents and data exclusivity are critical forms of the intellectual property essential to ensuring continued investment leading to

[41] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[42] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[43] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[44] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

[45] Grabowski, HG and Kyle, M, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 491-502 (28: 2007).

[46] See, for example, DiMasi, JA, and Paquette, C, "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and Timing of Development," *Pharmacoeconomics* 1-14 (22 Supp 2:2004).

critical medical breakthroughs. Data exclusivity associated with a follow-on biologics pathway should be at least 14 years, with additional exclusivity available for post-approval indications.

Patents and data exclusivity are both incentives for investment in innovation. They work in a complementary fashion. Patents reward an invention by providing the innovator with the right to prevent anyone else from making, using or selling the patented invention for a defined period of time. Data exclusivity recognizes the large-scale investment required to develop safety and effectiveness data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and effectiveness of its product. (Data exclusivity differs from market exclusivity because data exclusivity does not prevent an applicant from submitting an application and obtaining approval based solely on its own data. Market exclusivity would prevent approval of an application within the exclusivity period even if the applicant used its own data). Neither patents nor data exclusivity bar other innovators with competing, non-infringing drugs from the market.

As the Hatch-Waxman compromise for drugs reflects, patent protection is necessary but not alone sufficient to provide adequate incentives for medical innovation. Some of the patent life necessarily is lost during the time consumed by the extensive development and FDA approval process that is required to bring a new medicine to market, and patent term restoration provides only partial compensation for this lost time. Further, in the case of biologics, a product patent may provide insufficient protection if an FOB applicant can circumvent the patent under the similarity standard for FOB approval. Moreover, patents nearly always have a measure of uncertainty, but investments in the testing and clinical trials needed to obtain FDA approval must be made long before an innovator knows whether a patent may someday be successfully challenged. Data exclusivity provides a measure of certainty, allowing investments in clinical trials to be supported. Data exclusivity also provides an incentive for continued research leading to new indications post-approval and after patents have expired.

The uncertainty of patent protection, which emphasizes the need for data exclusivity, is evident in the research of Grabowski and Kyle (2007).[47] They found that the number of patent lawsuits associated with Paragraph IV filings has grown in recent years and that these legal challenges are occurring much earlier in the drug's lifecycle. Grabowski and Kyle (2007) conclude that these trends are shortening the average time that innovators have to attempt to recoup their research and development investment. According to Grabowski (2007), "[m]ost of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an ANDA filing with a paragraph IV certification."[48] Grabowski (2007) concludes that these challenges and the accompanying "uncertainty adversely impacts biopharmaceutical research and development resulting in firms abandoning research and development projects on future drug candidates with uncertain patent prospects. Early patent challenges also can have a chilling effect on the development of new indications and

[47] Grabowski, HG & Kyle, M, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 492 (2007).
[48] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

formulations, given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval."[49]

Duke University economist Henry Grabowski has calculated the appropriate period of data exclusivity for biologics as being 12.9 to 16.2 years, based on the estimated period of time it takes a portfolio of biologics marketed by a mature company to earn back the average cost of R&D needed to bring a new biologic to market.[50] We believe this and other research justifies a period of at least 14 years of data exclusivity for biologics. Additional exclusivity should be available for post-approval indications, in light of the central importance of post-approval research to achieving medical progress and the investment needed to support the clinical trials required to obtain an FDA-approved new indication.

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?**

Biotechnology has emerged as an engine of innovation, with benefits for patients and the economy. With scientific knowledge about the molecular basis of disease developing rapidly, the opportunities to maintain and expand this engine of innovation are strong. Medical advances created by the biotechnology sector are achieving significant progress against a range of serious diseases, such as leukemia, breast and colon cancer, rheumatoid arthritis, multiple sclerosis, and a range of rare diseases. Fortunately, there is opportunity for further innovation and treatment advances that can change the course of diseases that have been without effective treatments, based on the growing scientific understanding of disease at the molecular level. In addition to the human benefits, future medical advances can generate important economic benefits. For example, research conducted for the Alzheimer's Association projects that developing new treatments that delay the onset or slow the progression of Alzheimer's disease by five years could save $100 billion per year by 2020 in Medicare and Medicaid costs alone.[51] Progress of this type will come only from innovative medicines, many of which will be biologics, not FOBs or generic small molecule drugs.

An FOB pathway without incentives beyond existing patent protections would be insufficient to create an environment for sustained innovation. As discussed in our responses under "Patents" and "Incentives/Exclusivity/Investment" Question 1, we believe that a data exclusivity period of at least 14 years in addition to patent protection is needed to sustain innovation. If a pathway were created and there were no changes to the patent laws, there would not clearly be a statutory artificial act of infringement for filing BLAs. This creates a risk that one may not be able to resolve patent disputes prior to the data exclusivity period expiring, or at least the

[49] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[50] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[51] Lewin Group. Saving Live, Saving Money: Dividends for Americans Investing in Alzheimer's Research. Falls Church: VA: The Lewin Group, 2004.

marketing of the FOB, which is discussed in "Patents" Question 4. Regarding potential alternative incentives, simply put, there is no meaningful record of any alternative incentive that could replace patents and data exclusivity as a basis for this research and development enterprise that brings medicines to patients. Further, pediatric exclusivity and exclusivity for orphan indications is necessary to provide incentives for R&D investment. In addition to extraordinary science, the biopharmaceutical sector depends upon patents and data exclusivity to bring new medicines from the lab to patients. For more detail on the importance of intellectual property in generating and sustaining the investment needed for continued medical advances, please see our responses to the "Patents" and other "Incentive/Exclusivity/Investments" questions. Some of the potentially negative effects on innovation and the biotechnology sector if there are not ample incentives for innovation are briefly discussed below.

The Economic Competitiveness of the Biopharmaceutical Sector May Diminish--

The U.S. manufacturing sector as a whole is facing increasing competition globally. Private investment now flows across national borders as investors seek the highest returns on their investment, and weak intellectual property protections may result in investment shifting overseas. Indeed, a government report focusing on increasing the global competitiveness of the U.S. manufacturing sector identifies as a key priority creating incentives for investment, including research and development.[52]

Currently, the U.S. is the clear global leader in biotechnology investment, jobs, and product development, offering opportunities for high-quality and robust economic growth, as reflected in the chart below:

2007 Biotechnology Sector Statistics (Total Industry)					
	USA	**Europe**	**Asia/ Pacific**	**Canada**	**Total**
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Analysis by Burrill and Company for PhRMA based on publicly available data, April 2008.					

In 2007, the U.S. led the world in terms of the number of compounds in development with 2,742 - more than 1,000 more than the rest of the world combined and almost twice the number under development in Europe.[53] However, if there are insufficient incentives for innovation, R&D investment may shift away from the U.S. just as it shifted away from Europe in the 1990s. In the

[52]U.S. Department of Commerce, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers" (2004).
[53] PhRMA, Pharmaceutical Industry Profile (Mar 2008) *available at* http://www.phrma.org/files/2008%20Profile.pdf.

1990's, the United States surpassed Europe as the leading site for pharmaceutical research and development. This increased investment in research and development in the United States is reflected in the fact that "in the late 1980s only 41% of the top 50 innovative drugs were of American origin, in the late 1990s…[it had] climbed to 62%."[54]

Weak intellectual property protections would adversely affect U.S. competitiveness by diminishing the incentives for research and development investment. The resulting uncertainty and litigation costs from weak intellectual property protections would increase risks and diminish research and development investment funding sources for this sector. According to Grabowski (2007), the majority of the biotechnology industry is dependent on venture capital and "venture capital firms are agnostic about which industries they invest in, and can shift to information technology companies or even a new fast food chain if there is heightened uncertainty about returns from biopharmaceutical firms."[55] Not only could investment shift from one sector to another but investment could shift from the U.S. to other regions of the world, such as the Asia-Pacific region. Ernst & Young reports that the biotechnology sector is growing rapidly in countries in the Asia-Pacific region, where countries have stated they are going to take measures to boost intellectual property protection and promote competition for domestic industries to foster the biotechnology sector.[56]

Venture Capital and Other Investors Could Shift Funding to Other Sectors—
As the chart illustrates, in 2007, the U.S. accounted for more than one-half of the world's biotechnology employees. Some observers may believe that the biotechnology sector is so economically strong that it could easily weather weakened incentives for innovation while maintaining its innovative capacity and the scale of its R&D enterprise. However, this conclusion does not consider how various approaches to develop an abbreviated pathway for FOBs may affect this sector nor does it reflect the nature of this sector. There have been considerable successes, reflecting the opportunity to earn a return by beating the odds by having a valuable product progress through clinical trials (where the large majority of products fail), receive FDA approval, and become widely accepted in the market. But the industry also has had many failures, with companies investing venture capital and publicly raised funds for decades without achieving an approved drug. Biotechnology has been characterized as "one of the biggest money-losing industries in the history of mankind….," losing nearly $100 billion since 1976.[57] In fact, *The New York Times* reports that only 54 of the 342 publicly traded biotechnology U.S. companies were profitable in 2006.[58]

According to the National Venture Capital Association, "[l]arge successful companies such as Genentech, Amgen, and countless smaller innovative life sciences companies may never have gotten off the ground if not for the venture capital support received in the early stages of their

[54] Verheugen, G, "Future Post G-10 Pharmaceutical Strategy," speech at the Annual Meeting of the European Federation of the Pharmaceutical Industry and Association (Apr. 14, 2005).
[55] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[56] Ernst & Young, "Beyond Borders: A Global Perspective" (2006).
[57] Pisano, G, "Science Business: the Promise, the Reality, and the Future of Biotech" (Harvard Business School Press 2006).
[58] Pollack, A, "It's Alive! Meet One of Biotech's Zombies," *The New York Times* (Feb. 11, 2007).

development."[59] Due to the uncertainty, high-risk nature, and costs associated with biologics development, venture capital investment is often the only funding option for small firms. In fact, 70% of small biotechnology firms never become profitable, even after more than 20 years in business.[60] This is not to suggest that the sector should be viewed negatively — again, it has had real successes — but rather that incentives matter to its continued ability to attract the resources needed for a large scale biomedical research enterprise that can deliver the medical advances society needs and desires. Venture capitalists could shift funding to other sectors as their investment is based on the rationale that whereas the "majority of their high risk early stage investments will fail … strong returns on a few successful projects are often enough to justify investments in high risk endeavors that entail many losses" (Grabowski 2007).[61] Ernst & Young (2006) report that since 2002, venture capitalists have become more risk adverse and have shifted to later-stage, product focused alliances, which they say reflects an investment focus on expected returns within their investment horizons, but may negatively impact the biotechnology industry's long-term viability.[62] This trend would likely be exacerbated if an abbreviated pathway for FOBs provides insufficient incentives for innovation.

Without Robust Innovation Incentives, the Number of New Biologics and New Indications for Existing Biologics Will Likely Decline - New medicine development is a lengthy process, and total development time has grown significantly. The average development time has increased from approximately eight years as of 1960, to between 10 and 15 years.[63] The research and development process is also very risky, with few drugs or biologics surviving the rigorous development process. For every 5,000 to 10,000 compounds tested, just five will make it to clinical trials and, of those, and only one will eventually receive FDA approval.[64] Further, for those drugs or biologics that do reach human clinical trials, clinical trial protocols have become far more demanding and complex. In addition to increases in the number of clinical studies performed, the number of unique procedures per protocol has increased, as have the criteria for enrollment and the time to conduct clinical trials.[65]

Accordingly, the average cost to develop a new medicine is now estimated to be more than $1.2 billion.[66] Despite popular misconceptions about the invariable profitability of biopharmaceutical companies, only two in 10 approved medicines bring in enough revenue to recoup the cost of development. [67] These dynamics reinforce the importance of strong intellectual property

[59] National Venture Capital Association, "Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation" (2007).
[60] Pollack, A, "It's Alive! Meet One of Biotech's Zombies," *The New York Times* (Feb. 11, 2007).
[61] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf
[62] Ernst & Young, "Beyond Borders: A Global Perspective" (2006).
[63] DiMasi, JA and Grabowski, HG, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 469-79 (June 2007).
[64] PhRMA, "Drug Discovery and Development: Understanding the R&D Process," *available at* www.innovation.org.
[65] Tufts University Center for the Study of Drug Development, "Growing Protocol Design Complexity Stresses Investigators, Volunteers," Tufts Impact Report (Jan/Feb 2008).
[66] DiMasi, JA and Grabowki, HG, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 469-79 (June 2007).
[67] Vernon, J, Golec, R and DiMasi, J, "Drug Development Costs When Financial Risk is Measured Using the FAMA-French Three Factor Model," unpublished working paper (2008).

protection and appropriate incentives to ensuring a vital, innovative biopharmaceutical industry. In the absence of strong intellectual property protections, Kaitin (2008) suggests that research programs focused on developing biologics for more chronic and complex diseases could be discontinued, as these areas of research are particularly challenging, costly, and uncertain. Similarly, Grabowski (2007) says that neither innovator companies nor generic drug or FOB manufacturers would be able to grow and prosper, as the rate of new product introductions would decline dramatically.[68] In conclusion, without data exclusivity and adequate patent protection, innovators would be less likely to invest in developing and marketing new medicines with few remaining years of patent protection or with uncertain forms of protection. If a pathway were created without data exclusivity, it could negatively affect current and future investment in this sector.

Incentives for Universities and Other Research Institutions to Partner With the Private Sector Would Decline - Universities own a large number of patents on basic research on biologics and license many patents to biopharmaceutical companies, emphasizing the centrality of intellectual property throughout the life sciences innovation system. Historically, collaborative efforts of research universities and biopharmaceutical companies have led to important medical innovations; continued innovation would be threatened without adequate intellectual property incentives. The American Association of Universities (AAU)[69] has stated that:

- Without a "period of exclusivity commensurate with the attendant risk, such investments will become an irrational business decision, and the companies which make these investments will cease to do so, sharply reducing the transfer of basic research discoveries from universities and other research institutions into product development."

- The negative impact on innovation would be felt by universities as they would have "great difficulty finding a partner to bring early-stage research to next-phase development."

- The lack of sufficient incentives would make "it even more difficult to transfer new knowledge to the private sector for development in to products that can benefit patients."

As discussed previously, the cycle of investment and innovation in the biotechnology sector requires strong and certain intellectual property rights to protect the innovation itself and to foster the circumstances that make innovation possible.

[68] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[69] Letter from the American Association of Universities to Sen. Edward M. Kennedy and Sen. Michael B. Enzi (June 18, 2007), *available at* http://www.aau.edu/intellect/Ltr_Berdahl_Kennedy_Biologics_61807.pdf; http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

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.**

Experts predict that FOBs are likely to have lower research and development costs than innovator biologics and potentially to intensify price competition and yield modest cost savings over the cost of innovator biologics. The lower potential costs would be due in part to proposed legislation allowing a FOB manufacturer to rely in part on the safety and effectiveness of the innovator to gain FDA approval. To date, a number of organizations have tried to quantify the potential savings from creating an abbreviated pathway for approval of FOBs. Most of these efforts focused on assessing the potential cost savings based on the parameters outlined in "The Access to Life-Savings Medicines Act" (H.R. 1038/S. 623), which vary from the parameters of subsequent legislative proposals. Most of these modeling efforts focused on estimating the timing of FOB entry, market uptake, and discounting levels, because these are key drivers that influence the ultimate level of savings. The results of this research have yielded vastly different estimates because they are based on assumptions around which there is significant uncertainty and/or because they use clearly erroneous assumptions that inflate projected savings. Some of the key uncertainties are outlined in the table below:

Significant Uncertainties Exist when Predicting Economic Impact	
Timing	Passage of legislation, issuance of implementing regulations, and readiness of FOB manufacturers are all unknown.
Clinical Trial Requirements	Uncertainty regarding the nature and extent of clinical testing requirements for FOB manufacturers.
Patent Expiry	Publicly available information on patent expiry varies widely in terms of accuracy and completeness.
Pricing	Lack of substantial experience with follow-ons in U.S. biologics market and little international data to support assumptions.
Market Entry	Extent of FOB competition and degree to which new brand or innovator biologics entering a class may be affected by how the legislation shapes the regulatory pathway, the future competitive landscape, and untested pricing models.
FOB Uptake	The degree to which patients and physicians will accept FOBs is unclear.

Carefully done studies, relying on the most realistic assumptions and best available data, include the following:

- Henry Grabowski, Ph.D. Grabowski's work uses historic biopharmaceutical data to simulate market entry rates and corresponding price discount levels. His work shows that with few FOBs on the market, a likely scenario in the first years after a regulatory pathway is created is that potential price discounts will be small. While he did not publish a precise savings estimate (predicting only "several billion in

savings"), he indicated savings would likely be lower than the estimate developed by Avalere Health.[70]

- Avalere Health, LLC. This "CBO-style" estimate calculated $3.6 billion in Federal savings over 10 years.[71] While the Avalere analysis provides a realistic timeframe for development of the regulations and guidance for an FOB regulatory pathway, there is considerable uncertainty regarding the projections of potential market share for FOBs based on the issues raised above.

- Howrey/CAP Analysis. This study added to the debate by reviewing the credibility and likelihood of accuracy of the assumptions made by Engel & Novitt and Express Scripts. Given the amount of uncertainty around market entry, inaccuracies in patent expiration dates, and degree of potential discounts, the Howrey/CAP Analysis research sought to correct specific errors in assumptions made and re-estimated savings claimed in these two studies at between $2 to $2.8 billion over a 10-year time period.[72]

It is evident that "scoring" FOB legislation over a 10-year period is challenging; the further out the estimates, the more uncertainty that surrounds the estimates. However, the estimates in the studies referenced above are valuable because they systematically and carefully develop a comprehensive analytic framework. These frameworks include the potential relationship between the number of potential FOB competitors and price discounts and the likely time lag between passage of a bill and promulgation of regulations. Though significant uncertainty exists for each assumption, these estimates are based on actual data points, and where uncertainty exists, take a midpoint estimate or a conservative estimate.

Studies that Clearly Overestimate Projected Savings

While it is unclear at this time exactly how the market for biologics will develop, there are enough data points to assess the feasibility of the savings estimates in other published studies. For example, while we do not know when Congress will pass FOB legislation, for the reasons referenced above it is highly unlikely that in the first year of passage the federal government and other payers would experience savings. Yet this is the assumption made in numerous analyses. Studies falling into the category of overestimating savings include those by Engel & Novitt, LLP,[73] Express Scripts,[74] Robert Shapiro et al,.[75] and Everett Ehrlich.[76] We do not intend to

[70] Grabowski, HG, et al., "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007).
[71] Avalere Health LLC, "Modeling Federal Cost Savings from Follow-On Biologics" (Apr. 2007), *available at* http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf.
[72] Howrey & CAP Analysis, "The Inflated Projections of Potential Cost Savings from Follow-On Biologics: An Analysis of the Express Scripts and Engel & Novitt Reports" (May 2007).
[73] Engel & Novitt LLP, "Potential Savings that Might be Realized by the Medicare Program from Enactment of Legislation Such As the *Access to Life-Saving Medicine Act* (H.R. 6257/S. 4016) that Establishes a New BLA Pathway for Follow-on Biologics," *Pharmaceutical Care Management Associates* (Jan. 2007).
[74] Miller, S, & Houts, J, "Potential Savings of Biogenerics in the United States," *Express Scripts* (Feb. 2007).
[75] Shapiro, R, Singh, K & Mukim, M, "The Potential American Market for Generic Biological Treatments and the Associated Savings," *Insmed Corporation* (Feb. 2008).

suggest that legislation creating an FOB pathway, while assuring safety and continued innovation, would be devoid of savings. Rather, a realistic view underscores that policymakers should not jeopardize patient safety and continued innovation in return for exaggerated claims of savings.

A number of flawed assumptions lead to inflated estimates. Key flawed assumptions are briefly discussed below. First, the studies incorrectly assume the market for FOBs will mirror the market for generic pharmaceuticals. Research suggests there will be fewer FOB entrants than seen for small molecule generics;[77] the costs of entry will be higher and as a consequence, fewer firms will enter, and average prices will decline less for FOBs than for generic drugs;[78] there will likely be a slow uptake of FOBs at least in the short term due to physicians', patients', and payers' lack of experience with FOBs;[79] and FOB manufacturers will have a learning curve in bringing biologics to market and may need to develop sales forces, which would slow market penetration rates.[80] Assuming immediate and large savings, as these studies do, is not realistic; doing so inflates savings. Second, many of these studies assume patent expiry earlier than has been publicly reported by manufacturers. Therefore, these models assume market entry for FOBs earlier in the 10-year budget window than is realistic. Third, the complexity of manufacturing and the substantial manufacturing costs are also likely to impact the number of FOB entrants. FOBs are projected to have higher development costs, as at least some level of clinical testing will be necessary to establish the safety and effectiveness of FOBs. The degree to which such requirements will impact the costs of bringing FOBs to market and their eventual pricing is unknown at this time. In sum, potential savings from FOBs are likely to be modest over a 10-year time period.

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?**

This question is not applicable to PhRMA.

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

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[76] Erlich, E, "Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers," *Citizens Against Government Waste* (May 2007).
[77] Grabowski, HG, et al., "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), available at http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.
[78] Statement of Henry G. Grabowski, Ph.D., Duke University, before the H. Comm. on Oversight and Government Reform 8-9 (Mar. 26, 2007), *available at* http://oversight.house.gov/story.asp?ID=1223.
[79] Statement of Henry G. Grabowski, Ph.D., Duke University, before the H. Comm. on Oversight and Government Reform 8-9 (Mar. 26, 2007), *available at* http://oversight.house.gov/story.asp?ID=1223.
[80] Bernstein Research, "Biogenerics: Long Rainbow, Small Pot of Gold; Limited Risk for Biotechs" (Oct. 2006).

As discussed further below in "Economic Impact" Question #5, the U.S. biotechnology sector makes important economic contributions to the United States, contributions likely to grow if the underpinnings for large-scale investment in the sector remain intact. U.S. competitiveness and leadership in this sector are likely to continue if an FOB pathway is established that recognizes the importance of assuring patient safety and maintaining strong incentives, including strong intellectual property, for innovation. A pathway that does not meet these objectives would put continued U.S. global leadership at risk. The U.S. is recognized for its leadership on strong intellectual property rights and innovation in the biotechnology sector, but this role would be significantly diminished if an FOB pathway is established with insufficient intellectual property incentives for the investment needed to seize the extraordinary opportunities for medical advances and economic growth offered by this 21st Century knowledge-based sector.

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?**

For the reasons discussed in our responses to the Committee's "Patent" and "Incentives/Exclusivity/Investment" questions, patents are a necessary and important intellectual property incentive in the biopharmaceutical research and development process. To serve this role well, patent-related rules must provide efficient, predictable, and meaningful protection and enforcement. The treatment of patents must allow the full range of intellectual property protection available under U.S. law to be obtained and enforced and for economically efficient intellectual property transactions and dispute settlement.

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?**

Biotechnology has emerged as an engine of innovation, with benefits for patients and the economy. With scientific knowledge about the molecular basis of disease developing rapidly, the opportunities to maintain and expand this engine of innovation are strong. Medical advances created by the biopharmaceutical sector are achieving significant progress against a range of serious diseases, such as leukemia, breast and colon cancer, rheumatoid arthritis, multiple sclerosis, and a range of rare diseases. Fortunately, there is opportunity for further innovation and treatment advances that can change the course of diseases that have been without effective treatments, based on the growing scientific understanding of disease at the molecular level. In addition to the human benefits, future medical advances can generate important economic benefits. For example, research conducted for the Alzheimer's Association projects that developing new treatments that delay the onset or slow the progression of Alzheimer's disease by five years could save $100 billion per year by 2020 in Medicare and Medicaid costs alone.[81] Progress of this type will come only from innovative medicines, many of which will be biologics, not FOBs or generic small molecule drugs.

An FOB pathway without incentives beyond existing patent protections would be insufficient to create an environment for sustained innovation. As discussed in our responses under "Patents"

[81] Lewin Group. Saving Live, Saving Money: Dividends for Americans Investing in Alzheimer's Research. Falls Church: VA: The Lewin Group (2004).

and "Incentives/Exclusivity/Investment" Question 1, we believe that a data exclusivity period of at least 14 years in addition to patent protection is needed to sustain innovation. If a pathway were created and there were no changes to the patent laws, there would not clearly be a statutory artificial act of infringement for filing BLAs. This creates a risk that one may not be able to resolve patent disputes prior to the data exclusivity period expiring, or at least the marketing of the FOB, which is discussed in "Patents" Question 4. Regarding potential alternative incentives, simply put, there is no meaningful record of any alternative incentive that could replace patents and data exclusivity as a basis for this research and development enterprise that brings medicines to patients. Further, pediatric exclusivity and exclusivity for orphan indications is necessary to provides incentives for R&D investment. In addition to extraordinary science, the biopharmaceutical sector depends upon patents and data exclusivity to bring new medicines from the lab to patients. For more detail on the importance of intellectual property in generating and sustaining the investment needed for continued medical advances, please see our responses to the "Patents" and other "Incentive/Exclusivity/Investments" questions. Some of the potentially negative effects on innovation and the biotechnology sector if there are not ample incentives for innovation are briefly discussed below.

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[82]U.S. Department of Commerce, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers" (2004).

In 2007, the U.S. led the world in terms of the number of compounds in development with 2,742—more than 1,000 more than the rest of the world combined and almost twice the number under development in Europe. [83] However, if there are insufficient incentives for innovation, R&D investment may shift away from the U.S. just as it shifted away from Europe in the 1990s. In the 1990's, the United States surpassed Europe as the leading site for pharmaceutical research and development. This increased investment in research and development in the United States is reflected in the fact that "in the late 1980s only 41% of the top 50 innovative drugs were of American origin, in the late 1990s.…[it had] climbed to 62%."[84]

Weak intellectual property protections would adversely affect U.S. competitiveness by diminishing the incentives for research and development investment. The resulting uncertainty and litigation costs from weak intellectual property protections would increase risks and diminish research and development investment funding sources for this sector. According to Grabowski (2007), the majority of the biopharmaceutical industry is dependent on venture capital and "venture capital firms are agnostic about which industries they invest in, and can shift to information technology companies or even a new fast food chain if there is heightened uncertainty about returns from biopharmaceutical firms."[85] Not only could investment shift from one sector to another but investment could shift from the U.S. to other regions of the world, such as the Asia-Pacific region. Ernst & Young reports that the biotechnology sector is growing rapidly in countries in the Asia-Pacific region, where countries have stated they are going to take measures to boost intellectual property protection and promote competition for domestic industries to foster the biotechnology sector.[86]

Venture Capital and Other Investors Could Shift Funding to Other Sectors—
As the chart illustrates, in 2007, the U.S. accounted for more than one-half of the world's biotechnology employees. Some observers may believe that the biotechnology sector is so economically strong that it could easily weather weakened incentives for innovation while maintaining its innovative capacity and the scale of its R&D enterprise. However, this conclusion does not consider how various approaches to develop an abbreviated pathway for FOBs may affect this sector nor does it reflect the nature of this sector. There have been considerable successes, reflecting the opportunity to earn a return by beating the odds by having a valuable product progress through clinical trials (where the large majority of products fail), receive FDA approval, and become widely accepted in the market. But the industry also has had many failures, with companies investing venture capital and publicly raised funds for decades without achieving an approved drug. Biotechnology has been characterized as "one of the biggest money-losing industries in the history of mankind….," losing nearly $100 billion since 1976.[87] In fact, *The New York Times* reports that only 54 of the 342 publicly traded biotechnology U.S. companies were profitable in 2006.[88]

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[83] PhRMA, Pharmaceutical Industry Profile (2008) *available at* http://www.phrma.org/files/2008%20Profile.pdf.
[84] Verheugen, G, "Future Post G-10 Pharmaceutical Strategy," speech at the Annual Meeting of the European Federation of the Pharmaceutical Industry and Association (Apr. 14, 2005).
[85] Statement of Henry G. Grabowski, Ph.D., Duke University, before the H. Comm. on Oversight and Government Reform 8-9 (Mar. 26, 2007), *available at* http://oversight.house.gov/story.asp?ID=1223.
[86] Ernst & Young, "Beyond Borders: A Global Perspective" (2006).
[87] Pisano, G, "Science Business: the Promise, the Reality, and the Future of Biotech" (Harvard Business School Press 2006).
[88] Pollack, A, "It's Alive! Meet One of Biotech's Zombies," *The New York Times* (Feb. 11, 2007).

According to the National Venture Capital Association, "[l]arge successful companies such as Genentech, Amgen, and countless smaller innovative life sciences companies may never have gotten off the ground if not for the venture capital support received in the early stages of their development."[89] Due to the uncertainty, high-risk nature, and costs associated with biologics development, venture capital investment is often the only funding option for small firms. In fact, 70% of small biotechnology firms never become profitable, even after more than 20 years in business.[90] This is not to suggest that the sector should be viewed negatively — again, it has had real successes — but rather that incentives matter to its continued ability to attract the resources needed for a large scale biomedical research enterprise that can deliver the medical advances society needs and desires. Venture capitalists could shift funding to other sectors as their investment is based on the rationale that whereas the "majority of their high risk early stage investments will fail … strong returns on a few successful projects are often enough to justify investments in high risk endeavors that entail many losses" (Grabowski 2007).[91] Ernst & Young (2006) report that since 2002, venture capitalists have become more risk adverse and have shifted to later-stage, product focused alliances, which they say reflects an investment focus on expected returns within their investment horizons, but may negatively impact the biotechnology industry's long-term viability.[92] This trend would likely be exacerbated if an abbreviated pathway for FOBs provides insufficient incentives for innovation.

Without Robust Innovation Incentives, the Number of New Biologics and New Indications for Existing Biologics Will Likely Decline - New biopharmaceutical development is a lengthy process, and total development time has grown significantly. The average development time has increased from approximately eight years as of 1960, to between 10 and 15 years.[93] The research and development process is also very risky, with few biopharmaceuticals surviving the rigorous development process. For every 5,000 to 10,000 compounds tested, just five will make it to clinical trials and, of those, and only one will eventually receive FDA approval.[94] Further, for those biopharmaceuticals that do reach human clinical trials, clinical trial protocols have become far more demanding and complex. In addition to increases in the number of clinical studies performed, the number of unique procedures per protocol has increased, as have the criteria for enrollment and the time to conduct clinical trials.[95]

Accordingly, the average cost to develop a new medicine is now estimated to be more than $1.2 billion.[96] Despite popular misconceptions about the invariable profitability of biopharmaceutical

[89] National Venture Capital Association, "Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation" (2007).
[90] Pollack, A, "It's Alive! Meet One of Biotech's Zombies," *The New York Times* (Feb. 11, 2007).
[91] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf
[92] Ernst & Young, "Beyond Borders: A Global Perspective" (2006).
[93] DiMasi, JA & Grabowki, HG, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 469-79 (June 2007).
[94] PhRMA, "Drug Discovery and Development: Understanding the R&D Process," *available at* www.innovation.org.
[95] Tufts University Center for the Study of Drug Development, "Growing Protocol Design Complexity Stresses Investigators, Volunteers," Tufts Impact Report 1 (Jan/Feb 2008).
[96] DiMasi, JA & Grabowki, HG, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 469-79 (June 2007).

companies, only two in 10 approved drugs bring in enough revenue to recoup the cost of development. [97] These dynamics reinforce the importance of strong intellectual property protection and appropriate incentives to ensuring a vital, innovative biopharmaceutical industry. In the absence of strong intellectual property protections, Kaitin (2008) suggests that research programs focused on developing biologics for more chronic and complex diseases could be discontinued, as these areas of research are particularly challenging, costly, and uncertain. Similarly, Grabowski (2007) says that neither innovator companies nor generic drug or FOB manufacturers would be able to grow and prosper, as the rate of new product introductions would decline dramatically.[98] In conclusion, without data exclusivity and adequate patent protection, innovators would be less likely to invest in developing and marketing new medicines with few remaining years of patent protection or with uncertain forms of protection. If a pathway were created without data exclusivity, it could negatively affect current and future investment in this sector.

Incentives for Universities and Other Research Institutions to Partner With the Private Sector Would Decline - Universities own a large number of patents on basic research on biologics and license many patents to biopharmaceutical companies, emphasizing the centrality of intellectual property throughout the life sciences innovation system. Historically, collaborative efforts of research universities and biopharmaceutical companies have led to important medical innovations; continued innovation would be threatened without adequate intellectual property incentives. The American Association of Universities (AAU) [99] has stated that:

- Without a "period of exclusivity commensurate with the attendant risk, such investments will become an irrational business decision, and the companies which make these investments will cease to do so, sharply reducing the transfer of basic research discoveries from universities and other research institutions into product development."

- The negative impact on innovation would be felt by universities as they would have "great difficulty finding a partner to bring early-stage research to next-phase development."

- The lack of sufficient incentives would make "it even more difficult to transfer new knowledge to the private sector for development in to products that can benefit patients."

As discussed previously, the cycle of investment and innovation in the biotechnology sector requires strong and certain intellectual property rights to protect the innovation itself and to foster the circumstances that make innovation possible.

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[97] Vernon, J, Golec, R & DiMasi, J, "Drug Development Costs When Financial Risk is Measured Using the FAMA-French Three Factor Model," unpublished working paper (2008).
[98] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.
[99] Letter from the American Association of Universities to Sen. Edward M. Kennedy and Sen. Michael B. Enzi (June 18, 2007), *available at* http://www.aau.edu/intellect/Ltr_Berdahl_Kennedy_Biologics_61807.pdf; http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

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 EU biosimilar product-class specific guidelines are based on science and developed through expert consultation and public comment. They provide transparency and predictability for applicants and help protect patient safety. Such processes and guidelines would be similarly beneficial for a U.S. abbreviated pathway for approval of FOBs.[100]

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?**

The EU has recognized the importance of data exclusivity by establishing exclusivity periods for new drugs and biologics and by recognizing the need for additional periods of exclusivity for a significant new indication. While recognition of these principles is important, it also is necessary to recognize that economic analysis supports a more robust base period of data exclusivity for biologics in the U.S. as well as strong patent protection. Due to the unique aspects of the U.S. market, a base data exclusivity period of at least 14 years should be provided to innovator biologics. As discussed in "Incentives/Exclusivity/Investment" response to Question 1 and the responses to the "Patent" questions, research by Grabowski (2007)[101] states that based on the market dynamics in the U.S., a minimum data exclusivity period of 14 years is needed to recoup R&D investment and earn a risk-adjusted return on capital. An additional period of exclusivity should be provided for new indications.

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?**

As indicated above in response to "Incentives/Exclusivity/Investment" question 7, the United States is the global economic leader, by far, in the biologics sector, as measured by jobs, number of companies, number of products approved and in development, etc. This global leadership of a 21st Century knowledge-based sector with extraordinary innovative potential offers great promise to the U.S. economy, along with the likelihood that other nations will seek to challenge that leadership. The U.S. has a great opportunity to maintain its leadership and to see the sector realize its full potential as an engine of growth and medical advances due to the many favorable

[100] Please see answer #5 in the Regulatory/Administrative section for further information.
[101] Grabowski, HG, "Data Exclusivity for New Biological Entities," Duke University Department of Economics working paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

aspects of its environment for innovation. However, it is possible for nations to lose their competitive advantage. For example, as stated by EU Commission Vice President Günter Verheugen, "in 1990, the . . . pharmaceutical industry still invested 50% more in Europe than in the US . . . today, the same industry is investing 40% more in the U.S. compared to Europe. In 1992, 6 out of the 10 top medicines in worldwide sales were European, while in 2002 this figure had fallen to just 2."[102]

Empirical data show that research and development has shifted over time from Europe to the U.S., and experts say this is due in large part to the favorable environment for innovation in the U.S. If the U.S. were to adopt weaker incentives for innovation than those offered elsewhere, it is possible that research and development would shift to other countries with public policies more favorable to innovation. For more detail on how our Nation's competitiveness could be affected, please also see our response to "Incentives," Question 7.

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 abbreviated pathway for approval of biosimilars is currently the only such pathway governed by a robust regulatory system and as such should be considered when designing a similar pathway in the United States. Specifically, a reasoned approach, based on sound science, the primacy of patient safety, an open and transparent scientific consultation, and adequate opportunity for public comment are key principles that must be employed in the development of any abbreviated approval pathway for FOBs in the United States. Numerous other countries are incorporating key principles followed by the EU. The EU has approved or noted favorably biosimilars in three classes and rejected another, which is a testament to the utility of this pathway.

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?**

There is insufficient experience with biosimilars approved in the EU to assess their relative safety and effectiveness.

[102] Verheugen, G, "Future Post G-10 Pharmaceutical Strategy," speech at the Annual Meeting of the European Federation of the Pharmaceutical Industry and Association (Apr. 14, 2005).