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?**

2. **To what degree, if any, is immunogenicity testing necessary? Should immunogenicity testing be mandated by statute for all follow-on biologics (FOBs) or should the Food and Drug Administration (FDA) be given discretion to determine whether such studies, and what types of studies, are needed on a case- by-case basis?**

The answer below is in response to the two questions cited above.

Clinical safety testing, including immunogenicity testing, is necessary for the approval of every new biologic. Immunogenicity is the ability of a substance to stimulate an immune response. Virtually every marketed protein product stimulates an immune response in the body. For many biologics, immune responses may not be a concern because they may not result in clinically relevant effects. However, when clinically relevant immunogenic responses do occur, they can have very serious consequences, including anaphylactic shock which may rapidly lead to death. Patients also may develop autoimmunity to endogenous proteins, which means that the patient's immune response inactivates not only the medicine but also the naturally-occurring protein produced by the patient's body.

Immunogenicity is a special concern for biologics because our immune systems have evolved to be exquisitely sensitive to foreign biological substances, as a means of survival. At this time, no validated laboratory or non-clinical test system is available to predict whether a biologic produced by a new process will cause adverse immunologic consequences in patients. The difficulty of predicting immunogenicity from analytical and/or preclinical studies alone is demonstrated by the past experience of innovators, which reveals that, because a myriad of factors can affect immunogenicity, two biologics that are similar in molecular structure and composition may not have similar immunogenicity profiles.

The Food and Drug Administration (FDA) should have discretion to determine which types of clinical immunogenicity studies, and what amount of data, are needed, on a case-by-case basis. However, it is appropriate for Congress to require clinical immunogenicity testing for follow-on biologics to ensure safety and efficacy. To not require such testing could be detrimental to patient health.

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 exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes. This discretion is necessary because immunogenicity testing requirements will vary according to the type of manufacturing change, and the data the manufacturer has to demonstrate comparability between the product's attributes before and after the change. FDA appropriately exercises discretion because it is dealing with the manufacturer who has detailed knowledge and extensive experience in making this product.

However, immunogenicity testing should be mandated by statute for follow-on biologics because, among other reasons, the follow-on manufacturer's process will always be substantially different from that of the innovator. For example, the two manufacturers will begin with different source materials and cell lines and will develop specifications and process controls that are unique to those particular materials and processes.

Product comparability testing for intra-manufacturer changes only yields useful results because the manufacturer begins from its intimate and exhaustive knowledge of a process that has been shown to produce consistently a safe, pure, and potent finished product. When that manufacturer makes a manufacturing change, FDA can rely on extensive side-by-side comparison of the product made after a manufacturing change with the product made before the change. For example, the manufacturer and FDA are able to assess differences not only between the final products, but also between process intermediates. The manufacturer and FDA know whether other aspects of the process – such as assays, analytical procedures, and equipment – are the same or not. It is not possible for a different manufacturer to conduct this extensive side-by-side comparison.

We note that, even though an innovator biologics manufacturer can conduct such extensive comparisons of the product before and after a manufacturing change, FDA still may require manufacturers to assess the significance of a manufacturing change by conducting pre-clinical and clinical studies, including immunogenicity testing.

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?**

Follow-on biologics should be approved indication by indication because, for biologics, safety and effectiveness may vary from one indication to another. For example, one biologic might show similar immunogenicity in patients with cancer and in patients with hepatitis, while another "similar" biologic might show quite different immunogenicity in those two populations. Or, one biologic might be effective for both an acute and a chronic indication, while another "similar" biologic may not be effective for both. Likewise, the same biological product used for different indications or different patient populations may have different safety and efficacy profiles in the two cases.

These differences would not be detected, and could not be assessed for clinical relevance, without clinical studies for each indication in each patient population. Consequently, to protect patient health, Congress should not allow a FOB to be approved for any

indication for which analytical and appropriate clinical studies have not been completed, even for indications approved for the innovator reference product. This is also the position taken by the Administration:

> Sponsors of applications under section 351(k) should be required to demonstrate biosimilarity for all conditions of use for which the reference product is approved because biosimilars are supposed to perform the same way that the reference product does. If a product proposed for approval in a section 351(k) application behaved differently for the reference product in any indication, it would not be "highly similar."[1]

The European Commission's 2003 Directive relating to medicinal products for human use also specifies that, for each claimed indication of a biosimilar product, the safety and effectiveness must be separately demonstrated (see Directive 2003/63/EC).

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?**

At a minimum, the new drug-safety related authorities given to FDA by the Food & Drug Administration Amendments Act of 2007 (FDAAA) should apply to follow-on manufacturers. Indeed, the fact that these products presumably will undergo less extensive pre-market testing than innovator biologics argues in favor of granting the Secretary full flexibility with respect to post-market requirements for follow-on biologics. Further, given that follow-on products will be only similar to the innovator product and not the same, legislation should give the Secretary authority to require whatever post-market testing is necessary for a follow-on product, regardless of what was required for the innovator product. Post-market testing may be necessary, for example, to address safety concerns unique to the follow-on, or to address issues that have arisen because of scientific and medical knowledge gained since the approval and widespread use of the innovator product.

We note that, in the European biosimilars context, post-market surveillance ("pharmacovigilance") is required:

> Data from pre-authorisation clinical studies normally are insufficient to identify all potential differences. Therefore, clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment. ... Pharmacovigilance systems

[1] June 26, 2007 letter from Michael O. Leavitt, Secretary of Health and Human Services, to Senator Edward M. Kennedy [hereinafter, "HHS Letter"].

(as defined in the current EU legislation) and procedures (including traceability as described in the current EU guidelines) to achieve this monitoring should be in place when a marketing authorisation is granted. Any specific safety monitoring imposed to the reference medicinal product or product class should be taken into consideration in the risk management plan.[2]

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?**

Follow-on biologics should be required by statute to have non-proprietary names that are readily distinguishable from those of the innovator products, and to be prescribed using those distinct names. Follow-on biologics are "similar" but not "identical" to the innovator product, and their safety and effectiveness profiles may differ from those of the innovator's product. Assignment of the same non-proprietary name to a biological medicine and any follow-on versions may be taken to imply that these products are substitutable when they are not. In many states, pharmacy and dispensing rules do not always require a pharmacist to seek the prescriber's permission to substitute one biologic medicine for another, or to notify the physician once substitution has occurred. Indeed, only a few states even require that the fact of substitution be communicated to the patient. Without a way to distinguish among similar biologic medicines, manufacturers, physicians, patients, pharmacists, and regulators will not be able ensure that patients receive the specific product prescribed to them.

In addition, it is essential that physicians, patients, and drug safety authorities be able to distinguish among "similar" biologic medicines that are made by different manufacturers in order to ensure the traceability of product in the market place and facilitate robust pharmacovigilance. Without such distinct names, it will not be possible to easily trace or identify the source of an adverse reaction, or for manufacturers or regulators to exercise appropriate control – including product recall, for example – if a serious problem is identified.

With respect to the naming standard for any "interchangeable" follow-on biologics, our position is the same. Follow-on biologics are similar rather than the same as the reference product, and therefore all biologics should have distinct non-proprietary names.

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?**

[2] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/42832/05/), http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf

A follow-on biologic and the reference product must have the same mechanism of action. Two products that are known to have different mechanisms of action are self-evidently not similar. If the mechanism of action is known, the follow-on manufacturer must demonstrate that its product has the same mechanism of action as the innovator product.

As recognized by the Department of Health and Human Services (HHS), "biosimilars may be approved decades after the reference product, and over time the technology or methods to assess mechanism of action may have improved."[3] Accordingly, as HHS suggests, it would be reasonable for the 351(k) application to include information regarding "mechanisms of action that are known or can be reasonably determined."[4]

8. **How much variability in chemical structure is there in individual brand biologics: (1) batch-to-batch, and (2) as a result of manufacturing changes? What are the implications, if any, for FOBs testing requirements, naming, and interchangeability?**

The variation that occurs from batch to batch of an innovator product is always within a clearly defined narrow range and, more importantly, clinical trials always will have been conducted to demonstrate the safety and effectiveness of the innovator product within that range.

To ensure consistency in the characteristics of the final product, and consistent safety and effectiveness, the manufacturer employs many tools for ensuring that the product remains within the range tested in clinical trials. These tools are applicable to that manufacturer's process only. They include rigorous specifications and in-process controls for numerous aspects of the manufacturing process, such as source materials, intermediates, formulation, and storage conditions.

A follow-on manufacturer that begins with different source materials and uses different reagents, equipment, and processes from the innovator will develop different specifications and process controls. Because analytical testing (as we discuss below) is not sufficient to assess the safety and effectiveness of a biologic, clinical trials must be conducted to demonstrate the safety and effectiveness of the follow-on product made within the range delimited by the follow-on manufacturer's own specifications and process controls.

The fact that biologics made by different processes can be only similar, rather than the same, leads to the conclusion that follow-on products should have a distinct non-proprietary name. Please see our comments on naming above for further discussion of this point. With respect to interchangeability, please see our discussion of interchangeability below.

[3] HHS Letter.

[4] Ibid.

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?**

Clinical trial data are fundamental for evaluating the safety and effectiveness of a follow-on biologic and must be required as part of the approval process for such products.

This is because the analytical tools currently available are not sufficient to detect the small variations among biologics that can have an important impact on safety or efficacy. The active substances in biologics, which are made in living systems, are typically much larger, more complicated, more sensitive, and more difficult to characterize than those in chemical drugs. Because clinically relevant variation among these products may be undetectable using currently available analytical methods, it is well-established and accepted that clinical data are necessary to demonstrate their safety and effectiveness.

The European Union (EU) experience with approving follow-on biologics demonstrates that a determination that clinical data are essential for the approval of follow-on biologics is not an impediment to products reaching the marketplace. EU law and guidelines allow for abbreviations in the non-clinical and clinical testing where science and safety permit; however, to ensure patient safety, the EU has required clinical safety testing (including clinical trials for immunogenicity) and post-market surveillance – even for the "simplest" and best understood biologics. Congress should at a minimum incorporate the requirements and safety protections included in the EU system into any pathway for approval of follow-on biologics in the United States.

We note that Congress previously has specified clinical study requirements for various types of approval in statute. The provisions of the Federal Food, Drug and Cosmetic Act (FFDCA) pertaining to the approval of innovative drugs, for example, specify "adequate and well-controlled investigations, including clinical investigations" (FFDCA Section 505(d)). Both precedent and scientific realities demand that Congress also specify the types of studies necessary to ensure the safety and effectiveness of follow-on biologics, i.e., Congress should require that clinical trial data be submitted to support approval of follow-on biologics. Further, patients and doctors will be less likely to utilize follow-on biologics if they do not have confidence in the requirements for testing these products in humans prior to market entry.

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?**

Under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA), an application must include (among many other things) "full reports of investigations which

have been made to show whether or not such drug is safe for use and whether such drug is effective in use."

To our knowledge there has been only one protein product approved under Section 505 without clinical trials. A menotropin (Repronex, made by Ferring) was approved under Section 505(j) of the FFDCA, the generic pathway, but was never distributed. Ferring chose to resubmit its application with clinical data under Section 505(b)(2).

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?**

This question is best answered by the manufacturer (Sandoz, a division of BIO member company Novartis).

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?**

It is BIO's longstanding position that there is not an approval pathway for follow-on biologics for reference products originally approved under Section 505 of the current Federal Food, Drug, and Cosmetic Act (for more information see our Citizen Petition at http://www.bio.org/healthcare/followon/BIO_CP--FINAL_DRAFT_4_22_03.pdf). Accordingly, Congress would have to affirmatively create such a pathway in order for FDA to approve follow-ons to such biologics.

2. **The current statute gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial. Do you think this statutory discretion has been appropriate or adequate? What has been its effect on patient safety?**

FDA's statutory discretion to decide whether a change in an approved biologic requires assessment through a clinical trial is appropriate. This discretion is necessary because clinical testing requirements (including immunogenicity testing requirements, as we discuss above) will vary according to the type of manufacturing change. However, clinical testing should be mandated by statute for follow-on biologics because the follow-on manufacturer's process will always be substantially different from that of the innovator. Among other things, the two manufacturers will begin with different source

materials and cell lines and will develop specifications and process controls that are unique to those particular materials and processes.

Product comparability testing for intra-manufacturer changes only yields useful results because the manufacturer begins from its intimate and exhaustive knowledge of a process that has been shown to produce consistently a safe, pure, and potent finished product. When that manufacturer makes a manufacturing change, FDA can rely on extensive side-by-side comparison of the product made after a manufacturing change with the product made before the change. For example, the manufacturer and FDA can assess differences not only between the final products, but also between process intermediates. The manufacturer and FDA know whether other aspects of the process – such as assays, analytical procedures, and equipment – are the same or not. This extensive side-by-side comparison is not possible for a different manufacturer to conduct.

We note that, even though an innovator biologics manufacturer can conduct such extensive comparisons of the product before and after a manufacturing change, FDA still may require manufacturers to assess the significance of a manufacturing change by conducting pre-clinical and clinical studies, including immunogenicity testing.

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

FDA review of follow-on biologics should be conducted by the same Review Division that approved the innovative product. The scientific expertise in the original Review Division is critical to ensuring safety and efficacy of the follow-on product.

4. **What standards are required to assure sufficient similarity between the FOB and the reference product? Is the requirement that the FOB be "highly similar" to the reference adequate or should an applicant be required to establish that the FOB is "as similar as scientifically as possible"? How would FDA assess these requirements?**

Neither the phrase "highly similar" nor the phrase "as similar as scientifically possible" is, standing alone, sufficiently precise or detailed to ensure the degree of similarity that should exist between a reference biologic and a follow-on. After the passage of follow-on biologics legislation, FDA implementation activities must follow to ensure that stakeholders have the detailed information necessary to meet the requirements in the law. These implementation activities must include the development, with public and stakeholder input, of guidance completed by FDA prior to approval of follow-on products in any specific area (please see our answer to the next question). Further, to ensure public confidence in this new system and these new products, FDA must work with all stakeholders to glean knowledge that will advance the agency's thinking about the appropriate requirements and the implications for patient safety.

5. **Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue and permit public comment on product-specific guidance**

before submission of applications? What are the advantages and disadvantages? How long will it take to put a regulatory framework in place, including new regulations and guidances for FOBs?

As with most new legislation, implementation activities are necessary – either by regulation or guidance that seeks public comment – to ensure that manufacturers have the detailed information necessary to meet the requirements in the law. With respect to follow-on biologics, which are an entirely new type of product (i.e., neither innovative nor generic), it is particularly important that FDA provide guidance prior to the approval of follow-on products. Because of the wide variety among types of biologics, it is essential that such guidance be specific to a particular product or product group.

The guidance development process, which includes the opportunity for public input, will have several important benefits. First, the provision of such guidance would provide for transparency with respect to agency decision-making, and such transparency is extremely important to public confidence in the safety of follow-on products. Second, the availability of such guidance will facilitate the development of follow-on biologics and, by providing an added degree of regulatory predictability, will likely encourage the entrance of more follow-on manufacturers to the market. Third, the opportunity for public input will allow innovators to contribute specific information gained from their lengthy experience in biologics manufacturing. Fourth, it would permit physicians, academics, and patients to provide valuable insights and data on the innovator product that might be relevant to the approval of follow-on products.

It is also important that the guidance-development process be conducted prior to product approvals because it would not make sense for FDA to engage in two potentially conflicting processes at the same time, i.e., simultaneously consulting stakeholders on the appropriate data requirements for follow-on biologics while approving specific follow-on applications that may or may not meet the data requirements ultimately established.

A requirement for public proceedings on guidance documents need not delay consideration of follow-on biologics. In most cases, the European Union has completed product-specific guidance in 12-18 months. While FDA must conduct its own guidance development process, it will have the benefit of what has been and can be learned from the European Union and, in some cases, this may allow FDA to complete guidance in a shorter time. Furthermore, we note that, after passage of follow-on biologics legislation, there are administrative processes FDA will have to put in place prior to approval of follow-on biologics; these will be separate from any guidance requirement. A guidance requirement would run concurrently with the establishment of these processes and thus would not create any additional delay.

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?**

This question is most appropriately answered by FDA. However, we note that user fees for traditional drugs and biologics now account for more than 59 percent of funding for FDA's human drug review, a 700 percent increase since 1993 when the program was first implemented. It is important that, whatever the source of funding for a follow-on biologics program, funding and fees now targeted to the review of innovative drugs and biologics should not be diverted.

Further, we note that the review burden associated with follow-on biologics is unlikely to be much less, and could in fact be more, than that associated with the review of an innovator product. The fees assessed should be commensurate with the work done by FDA, and therefore should not be less than the fees payable by innovators.

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?**

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

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.**

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?**

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

The answer below responds to the five questions cited above.

While the term "interchangeability" is used in many different and sometimes inconsistent ways, BIO's position is clear: BIO urges Congress to ensure that patients are not given follow-on biologics unless expressly prescribed by a physician.

In the context of follow-on biologics, "substitutability" would mean that, when a physician writes a prescription for an innovator biologic, a follow-on biologic may be (or even could be required to be by state law or insurance coverage) substituted for the

prescribed biologic at the pharmacy or dispensing level, without the physician or patient's knowledge or consent. Small molecule generic drugs can be designated as therapeutically equivalent and thus, in certain situations, may be dispensed in the place of innovator products without physician knowledge. In contrast, the current state of science does not support substitutability for biologics. Indeed, FDA recently stated:

> With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.[5]

If substitutability were permitted for biologics, patients might not only be dispensed a follow-on biologic rather than the prescribed biologic, but they might be switched back-and-forth among several products over time. Because generic versions of a drug are each the same in all meaningful respects to the reference product, switching among the innovator drug and its generic versions normally raises few concerns. However, switching among biologics that are "similar" – rather than the same – involves particular risks, as FDA also notes:

> For many follow-on protein products – and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.[6]

The European Medicines Agency (EMEA) and certain member states of the European Union have also recognized the fundamental differences between drugs and biologics with respect to substitutability. Recently, the EMEA issued a statement that "[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional." BIO believes that, consistent with the policies of EMEA and many European countries, patients should not be dispensed follow-on biologics unless expressly prescribed by a physician.

It is important to note that substitution has been a problem for certain small molecule generics as well. For example, levothyroxine, the generic form of certain medications treating hypothyroidism, is only safe and effective at a very narrowly defined dose. The American Thyroid Association has issued a public statement noting that patients should be alerted by their physicians or pharmacists that their levothyroxine preparation might be switched at the pharmacy, that patients should ask to remain on their current levothyroxine preparation, and that they should inform their physicians if their thyroid hormone is changed to a generic preparation because, following such a switch, thyroid function should be re-checked. If this kind of concern is evident even for small molecule generics, it is surely even more of a concern for large, complex biologics. The kinds and

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[5] http://www.fda.gov/cder/news/biosimilars.htm, Possible International Non-proprietary Name (INN) Policies for Biosimilars, September 1 2006.

[6] http://www.fda.gov/ola/2007/protein32607.html, Statement of Janet Woodcock, M.D., before House Committee on Oversight and Government Reform, March 26 2007.

sizes of studies that would have to be done to address doubts about substitutability – including the risks of switching – would be so large that the dataset presented for approval would likely be larger than that required to be presented by an innovator.

We also note that, even where two products have the same active ingredient and otherwise meet FDA's definition of "therapeutically equivalent," the products still may differ in other respects – such as release mechanisms, excipients, and storage conditions – *that are of particular importance when dealing with biologics*. As FDA notes in the Orange Book, "[w]hen such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity." Therefore it is dangerous to assume that, even if therapeutic equivalence could be established for biologics, substitution in the market place should be automatic.

We understand that patient groups and health provider groups also have expressed their concerns directly to the Committee about the possibility that a "follow-on biologic" might be substituted in the place of the therapy prescribed without the patient's knowledge or a doctor's permission. Furthermore, as Secretary Leavitt noted in his letter to Senator Kennedy:

> [I]n light of the current scientific limitations on the ability to make determinations for interchangeability, and because it is critical to protect patient safety, the Administration believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician, and legislation should not allow for determinations of interchangeability at this time.[7]

Given FDA's own acknowledgement that the current state of science is inadequate to show interchangeability with respect to complex biologics, Congress should, if – despite the limitations of current science – it decides to permit FDA to make interchangeability determinations for follow-on biologics, require that the agency publicly develop guidelines describing the requirements for demonstrating interchangeability with respect to that particular product or product group. As FDA notes, "FDA guidances are prepared to establish clarity and consistency in FDA policies, regulatory activities, and inspection and enforcement procedures."[8] Further, "they provide industry with specific details that often are not included in the relevant statutes and regulations, and ... help ensure that FDA's employees implement FDA's mandate in an effective, fair, and consistent manner."[9] **(**Please also see our comments on the FDA guidance development process in our answer to Question # 5 in the "Regulatory/Administrative" section above.)

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[7] HHS Letter.

[8] http://www.fda.gov/cder/mapp/4000-2_10_05.pdf, CDER MAPP 4000.2, p. 4.

[9] http://www.fda.gov/CbER/regsopp/8002.htm, CBER SOPP 8002, Section 3.

Finally, we caution that the term "interchangeability" is not defined by FDA and has no settled legal or regulatory meaning at this time. We note that some use this word to describe products that are not "substitutable" or "therapeutically equivalent," but which, under a physician's supervision, could be used to treat the same disease or condition in the same patient. We recognize that some biologics (including branded biologics) are already considered "interchangeable" in this limited sense. For example, the product labels for hepatitis B vaccines[10] contain some very limited statements about "immunological comparability" and the theoretical possibility of interchanging vaccines within a vaccination course. However, these products require a full data package to be approved, and do not meet FDA's definition of "therapeutic equivalents."

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

The degree of competition and potential cost savings arising from a follow-on biologics approval pathway is likely to be dependent on numerous factors, including product quality, cost of production, price discounting, market penetration, number of market entrants, potential market size for any given product, etc. For more detail, please see our answer in response to Question # 1 in the "Economic Impact" section below.

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?

In 1998, the Congressional Budget Office found that the average period of time for marketing of a drug product with patent protection is 11½ years.[11] A more recent, peer-reviewed study found that new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.[12]

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[10] The Recombivax label is available at http://www.merck.com/product/usa/pi_circulars/r/recombivax_hb/recombivax_pi.pdf, and statements about interchangeability may be seen in the section entitled "Interchangeability of Plasma-Derived and Recombinant Hepatitis B Vaccines." The Engerix-B label is available at http://us.gsk.com/products/assets/us_engerixb.pdf, and statements about interchangeability may be seen in the section entitled "Interchangeability With Other Hepatitis B Vaccines."
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[11] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

[12] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics, Volume: 28, Issue: 4-5, pages: 491-502 (2007).

2. **The Hatch/Waxman Act restored innovator patents up to 14 years, and further provided manufacturers with 5 years of data exclusivity. Is this a good model for biologic manufacturers? What lessons can we learn from the Hatch-Waxman Act, and apply towards Congress's discussion about FOBs?**

3. **Please explain if patents on biotech medicines will provide meaningful protection of intellectual property if a pathway is created to allow for the regulatory approval of FOBs? How do patents on biotechnological medicines compare or differ in the value they offer to traditional small-molecule drugs, if an FOB's pathway requires only that the FOB be highly similar to the reference product?**

The below response applies to the two questions cited above.

BIO believes that the balance between innovation and generic competition struck by the Hatch-Waxman Act can provide valuable insights for the development of a follow-on biologics approval pathway. The Hatch-Waxman Act provides innovators and generic competitors a range of statutory, patent, and litigation-based incentives that, as described in response to the previous question, operate to create de facto protection against generic competition for, on average, 13.5 years. However, to achieve that same balance in the follow-on biologics context, the mix of policy tools must be different because of the differences between small molecule drugs and biologics and differences between generic drugs and follow-on biologics.

Under the 1984 Hatch-Waxman Act, a generic version of a small molecule drug may be approved for marketing only if its active ingredient is the "same" as in the innovator product. Thus, the patents that cover the innovator's active ingredient generally will apply to the generic version. Accordingly, the generic drug manufacturer cannot gain FDA approval of its product by demonstrating that the active ingredient is the same as the innovator product and then claim in the patent context that it is different from the innovator's drug. In addition, the Hatch-Waxman Act contains provisions that can extend the term of an innovator patent to cover a period of 14 years following approval of an innovative drug. As noted above, new molecular entities today do not face generic market competition until 13.5 years post-FDA approval on average, evidencing that the mix of policy tools employed by the Hatch-Waxman Act has come remarkably close to achieving the 14-year mark deemed appropriate under the Act for innovators to recoup their substantial investments prior to generic entry.

In contrast, under the various statutory frameworks being considered for follow-on biologics, a follow-on will not be required to be the "same" as the innovator product due to the high degree of complexity of biologics. Instead, the follow-on product will only have to be similar or highly similar to the innovator product. The similarity standard for follow-on biologics creates a risk that a follow-on competitor will argue that it has "designed around" the innovator biotech patents – meaning that the follow-on may be outside of the scope of the innovator's patent claim. As a result, a follow-on biologic may be sufficiently similar to the innovator biologic to rely to some degree on the safety and

effectiveness of the innovator product and thus receive abbreviated regulatory approval. Yet, it may still be different enough from the innovator product to avoid a patent infringement claim and, thus, get on the market well in advance of innovator patent expiration.

The similarity standard exacerbates the existing challenge presented by the nature of biotech patents. Under rules of patentability specific to biotechnology inventions, patent claims on biologics must often be narrowly drawn to the specific innovative aspect (e.g., a specific protein or nucleotide sequence) to be allowable. By contrast, patents on small medicinal molecules can often claim a whole class (a so-called genus) of related molecular structures and thereby provide a "penumbra" of patent protection around the innovator small molecule. For these reasons, patents may provide less comprehensive protection for innovative biologics under a follow-on biologics regime than they do for small molecules in the generic drug context.

Accordingly, if data exclusivity in a follow-on biologics regime were limited to the 5 years under the Hatch-Waxman Act, it would severely undermine incentives to invest in biotech innovation. Instead, BIO believes that a 14-year period of data exclusivity should be granted for biologics in any follow-on biologics regime. Such an approach would ensure that biologics receive the same degree of effective market protection from follow-on competition that small molecules receive today from generics, as described above. For more detailed information, please see BIO's response to Question #1 in the "Incentives/Exclusivity/Investment" section below, as well as our white paper on exclusivity and patent protection in a follow-on biologics regime, found at the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

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?**

In order for the reference product or third-party patent holders to identify potential patent infringement claims, the FDA must issue a public notice when it receives a follow-on application, indicating the name of the reference product to which it relates. Then any party that believes the follow-on product could infringe on its patents should have the right to request, and obtain confidential access to, a copy of the follow-on application and supporting information on methods of production, in order to identify with particularity potentially infringed-upon patents. Following this exchange of information, a patent owner should notify the follow-on applicant of which patents it believes are infringed by the product or its production, and the follow-on applicant should respond by either agreeing to not seek approval of the product until the expiration of all such patents or with an explanation as to why it believes the asserted patents are in fact either invalid or not infringed. In the latter situation, the patent owners should be able to quickly bring suit for patent infringement in order to resolve these issues prior to the end of the exclusivity period and market launch of the follow-on product. Timely resolution of

patent disputes not only benefits patent owners, but also provides certainty to the follow-on manufacturer and avoids confusion in the marketplace by patients, physicians, and payers.

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?**

This should not be a question of balancing. Each relevant patent holder should receive adequate and timely notice of a follow-on application, with sufficient information upon which to make a judgment as to whether its patents may be implicated by such application. Further, each patent owner should be able to independently assert its patent rights under a process that is reasonably likely to be resolved prior to market launch of the follow-on product.

6. **Should a 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?**

While notification and exchange of patent-related information are critical in any follow-on biologics regime (see response to previous two questions), a patent listing system should not be required, and, in fact, would not be practicable with respect to follow-on biologics. Unlike small molecule drugs where listed innovator patents claim the active ingredient, the drug product, or its use for the labeled indication, and thus necessarily have a close nexus to the generic version, biologics generally have different types of patents that cover various aspects of a molecule, and often involve third-party platform patents as well. In addition, biologic patents are more often process-oriented (which are not even listable under the Hatch-Waxman Act), and it is not clear whether the follow-on biologics method of production might implicate such a patent – indeed, there may be a patent on a method of production that the follow-on manufacturer uses but the innovator does not. For these reasons, patent listing is not workable and not necessary. A process for notification and confidential exchange of information will accomplish the same result, with minimal burden on FDA's time and resources.

<u>Incentives/Exclusivity/Investment</u>

1. **Should reference product manufacturers be given a period of exclusive marketing in addition to the patent-term restoration already provided to them under Hatch-Waxman? If yes, how much is necessary to provide adequate incentives for innovation without unnecessarily delaying competition?**

The biotechnology industry in the U.S. is still relatively nascent and largely unprofitable: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small

companies – many of which will never see a product come to market or turn a profit – that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology companies (all biotechnology companies but the top ten) account for two-thirds of the industry's future clinical pipeline.*[13]

This enormous reservoir of biotech innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients. Thus, in crafting a follow-on biologics approval pathway, it is important to err on the side of incentivizing innovation, particularly in light of the unique elements of the biotechnology industry. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted follow-on biologics regime.

The statistics speak to the challenges this emerging industry faces. Biologics research and development is a high-risk endeavor, with higher capital costs, higher material costs, greater manufacturing costs and uncertainties, longer development times, and lower late-stage success rates than compared to small molecule drugs. In fact, from 2001–2005, the success rate of a Phase III trial for the average biotechnology product was just slightly more than 50%.[14] These failures occur at the last stage of product development – after years of research and hundreds of millions of dollars may have been spent.

The industry's heavy reliance on private equity also is notable. In 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:[15,16]

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Net Loss ($B)	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	4.1

Given these unique challenges, patent protection (even including patent term restoration under current law) is not sufficient to ensure adequate incentives for biotech innovation

[13] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

[14] Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.

[15] Ernst and Young LLP, Annual biotechnology industry reports, 1995 – 2006. Financial data based primarily on fiscal-year financial statements of publicly-traded companies.

[16] Only about 20 biotech companies are currently profitable: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

under a follow-on biologics regime. Rather, any statutory pathway for follow-on biologics must establish a substantial period of data exclusivity to preserve incentives for research, development, manufacture, and approval of new biologic therapies. This is necessary because, under a statutory framework allowing for follow-on biologics, there is a very real potential that the manufacturer of a follow-on product may be able to secure abbreviated regulatory approval based at least in part on the innovator's prior approval, and, at the same time, avoid infringing patents that protect the innovator's product. That likelihood exists because of the confluence of two critical factors not present in the Hatch-Waxman Act construct for generic small molecule drugs. First, unlike a generic drug which must be the same as an innovator product, a follow-on biologic will only be required to be "similar' or "highly similar" to the corresponding innovator product. Second, because of the nature of biologic products – large molecules produced by living cells and organisms – patent protection is often narrower and easier to "design around" than in the small molecule drug context.

In light of this potential gap in patent protection for biologics under a follow-on biologics regime, data exclusivity must be substantially longer than the five years currently afforded to small molecule drugs under the Hatch-Waxman Act. Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies must have some certainty that they can protect their investment in the development of new breakthrough therapies for a substantial period of time in order to secure the necessary resources from venture capital firms and other funding sources. Without sufficient data protection, companies and investors will have a great deal of uncertainty as to whether they will be able to recoup the – on average – $ 1.2 billion in research and development costs that are necessary to bring a biologic to market.[17] This large amount of uncertainty will cause companies and investors to direct their investments to other areas where there is a higher degree of certainty that they will obtain a fair return on their investment. If this occurs, society as a whole will suffer, as fewer cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions are developed.

BIO believes that the best data available support a 14-year period of data exclusivity – not an "exclusive marketing" period – for biologics under a follow-on biologics regime. Several independent factors support this position. First, we know that the breakeven point for return on investment in a biologic occurs after it has been on the market between 12.9 and 16.2 years,[18] and thus competition from follow-on biologics prior to that time period would clearly undermine incentives for such investment in the first place. Second, in 1984, Congress enacted patent term restoration provisions to provide pharmaceuticals with up to 14 years of patent protection following marketing approval.

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[17] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

[18] Grabowski, Henry. "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper. June 2007.

This time period was selected so that "research intensive companies will have the necessary incentive to increase their research and development activities."[19] As a result, the average period of time for marketing a drug product with patent protection now is 11.5 years,[20] and new molecular entities are, on average, marketed in the U.S. for 13.5 years before the entry of generic competition.[21]

Thus, any statutory formula that allows for follow-on biologics should at least guarantee the same degree of effective market protection that Congress found necessary to maintain incentives for innovation in small molecule drugs – and, for the reasons discussed above, that protection can be accomplished most predictably through data exclusivity. Indeed, if the data exclusivity period for biologics is less than the number of years available to drugs under patent term restoration (that is, 14 years), then, because of the patent protection gap and the higher risks of biologics development, it will skew investment away from biotech innovation.

In this sense, a 14-year period of data exclusivity for biologics would serve as an insurance policy that provides innovators with some certainty of protection. Because data exclusivity would run concurrently with the patent term for the product, it therefore would create actual protection only in those instances where the follow-on manufacturer would be able to work around the patents held by the innovator but still gain abbreviated approval of its product.

The presence of substantial data exclusivity also would serve as an additional incentive to research and prove the safety and effectiveness of new indications for existing biologics. Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time. It is important to provide substantial exclusivity for the original treatment in order to support the expensive further research and development for these later indications, as well as an additional period of exclusivity (e.g., two years beyond the standard 14-year period) to provide the proper incentives to obtain marketing approval for such indications.

For a fuller discussion of these data and the justification for 14 years of data exclusivity, please visit the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

[19] H.R. Rep. No. 98-857, at 41 (1984).

[20] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

[21] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics 28(4-5), pages: 491-502 (2007).

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?**

In order for a robust industry for the discovery and development of biologics to exist, companies must be certain that they will have adequate time to recoup their substantial R&D costs (on average $1.2 billion to bring a biologic to market[22]). The breakeven point for a biologic occurs after it has been on the market between 12.9 and 16.2 years.[23] If a company does not have adequate time to recoup its investment, it will not engage in the research and development of future products. Please also see BIO's answer and white paper listed in response to the previous question.

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

A second-generation product must go through the same rigorous FDA approval process as a first generation product. It requires development and submission of full clinical safety and efficacy data to support FDA review and approval of the complete marketing application (BLA or NDA). Accordingly, FDA approval of a second-generation product should be rewarded with full data exclusivity as well. Such exclusivity is necessary to enable manufacturers to invest in the development of such innovative modifications and to enable patients to benefit from these treatment advances. Simply put, without sufficient data exclusivity of their own, second generation products will not be developed if a follow-on biologics pathway is enacted. Such a result would be a "lose-lose-lose" situation. A loss for innovators who would not pursue product improvements, a loss for follow-on manufacturers who would not have second-generation products to select from, and most important, a loss for patients who would not have the benefit of improved products.

For new indications, there should be an additional data exclusivity period for the original innovative product (e.g., 2 additional years) as an incentive for innovators to invest in such advances. Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time. Without this additional exclusivity, there would be little incentive to research and obtain approval for these new indications.

BIO notes that data protection for a second-generation product will in no way affect the ability of a follow-on biologic to enter the market based on the original innovative product. The success of the second-generation product will depend on its incremental

[22] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

[23] Grabowski, Henry. "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper. June 2007.

benefits for patients in the face of the lower price of the follow-on to the first-generation product. If the second-generation product's benefit is minor in comparison to existing products, then it is unlikely – particularly in today's price-sensitive payer market – that granting data exclusivity to the second-generation product will impact the marketplace in any meaningful way. However, without any separate data exclusivity for second-generation products, major advances will be stymied.

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

It is important to emphasize that data exclusivity, as opposed to market exclusivity, does not prevent competition to innovator biologics. To the contrary, even with data exclusivity, a competitor is free to develop a similar product and gain FDA approval based on a full development program, if relevant patents have expired. Data exclusivity only protects against a competitor relying on the innovator product's safety and efficacy, as approved by the FDA, in obtaining approval of its own product.

Data exclusivity and patent protection serve different purposes, particularly so in a follow-on biologics regime. As discussed in response to previous questions, the differences between biologics and small molecule drugs, particularly with respect to the type of patent protection, mean that a follow-on sponsor may be able to obtain FDA approval in reliance on the clinical safety and effectiveness of the innovator product, yet avoid infringing the innovator's patents. Given that uncertainty, only data exclusivity can adequately protect an innovator from imminent follow-on competition. While a patent may protect against a competitor copying a specific aspect of an invention, only non-patent exclusivity in a follow-on biologics scheme can ensure that an innovator will be able to have a sufficient period of time to recoup its investment in the marketplace before other companies may rely on that investment in securing approval of competitor products.

Data exclusivity provides the certainty necessary to ensure investors and innovators that they will be able to recoup the – on average – $1.2 billion in research and development costs that are necessary to bring a biologic to market.[24]

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

Biologics should receive a period of data exclusivity substantially longer than the 5 years provided to small molecule drugs under the Hatch-Waxman Act. For our full response, please see our answers to question #1 above and questions #2 and #3 under the "Patents" section.

[24] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

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

BIO does not believe there are policy considerations that would justify principal reliance on patents to ensure innovation in the biotechnology industry under a follow-on biologics regime. As discussed above, non-patent exclusivity, i.e., data exclusivity, is critical to innovation and to the health of the biotechnology industry. Relying principally on patent protection, in a follow-on biologics scheme that does not require sameness but only similarity, will significantly undermine the incentives for biotechnology innovation.

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?**

When discussing future innovation, it is helpful to understand what biotechnological innovation has accomplished to date. Biotechnology has created hundreds of new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders, and many other rare and unmet medical conditions. In fact, between 1995 and 2005, 160 different medicines were approved to treat rare diseases that affect 200,000 or fewer patients. Biotechnology also is responsible for hundreds of medical diagnostic tests that keep the blood supply safe and detect other conditions early enough to be successfully treated.

This spectacular innovation depends on an environment where companies can attract the capital needed to continue massive R&D investment. Over the past 25 years, the average R&D intensity (R&D spending to total firm assets) for biotechnology was 38 percent. By comparison, the average R&D intensity for all industries was only about 3 percent.[25] According to Ernst and Young, "Global Year in Review 2006," the biotechnology industry has increased the amount of money it devotes to R&D by over 120% since 1994.[26] Biotechnology is one of the most research-intensive industries in the world. The U.S. biotech industry spent $19.8 billion on research and development in 2005 alone.

Most biotechnology companies depend on venture capital and other sources of private and public funding. Therefore, it is imperative to cultivate and preserve an environment in which companies can attract the capital needed to invest in the next generation of groundbreaking biotechnology treatments.

[25] Golec, Joseph H. and John A. Vernon. "Financial Risk in the Biotechnology Industry." NBER Working Paper 13604.

[26] Ernst & Young LLP, annual biotechnology industry reports, 1993–2006. Financial data based primarily on fiscal-year financial statements of publicly-traded companies; constant 2005 dollars.

For the reasons described in response to previous questions, patent protection (even including patent term restoration under current law) is not sufficient to ensure such adequate incentives under a follow-on biologics regime. Without sufficient non-patent protection, i.e., data exclusivity, biotech innovators and investors will have a great deal of uncertainty as to whether they will be able to recoup the – on average – $1.2 billion in research and development costs that are necessary to bring a biologic to market.[27] This large amount of uncertainty will cause companies and investors to direct their investments to other areas where there is a higher degree of certainty that they will obtain a fair return on their investment.

This decrease in biotechnology R&D investment will be detrimental not just to biotechnology companies, but also to American universities, as less of their cutting-edge research and fewer of their technologies will be licensed because companies will not be able to recoup the R&D investment necessary to take a licensed technology from the laboratory to the marketplace. Investors will turn to other less risky ventures, and cutting-edge research (including the substantial public investment in basic research through the National Institutes of Health) will sit on laboratory shelves, as it often did prior to the Bayh-Dole Act and the Hatch-Waxman Act patent term restoration provisions.

If this occurs, society as a whole will suffer. New treatments in the pipeline hold the promise of continued progress against our most pressing medical challenges. At present, more than 400 biotechnology medicines and vaccines are in development, targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis. Specifically, there are:

- 210 for cancer and related conditions
- 22 for cardiovascular disease
- 15 for diabetes and related conditions

These innovative treatments include:

- Monoclonal antibodies to treat asthma, Crohn's disease, and lupus
- Therapeutic vaccines for AIDS
- Recombinant proteins to treat autoimmune disorders

Without adequate incentives these – and many other – breakthrough cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions will either take longer to come to fruition or may not come to be realized at all.

In this regard, it bears emphasis that the biotechnology industry in the U.S. is still relatively nascent and largely unprofitable: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies – many of which will never see a product

[27] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

come to market or turn a profit – that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology companies (all biotechnology companies but the top ten) account for two-thirds of the industry's future clinical pipeline.*[28] *Yet it is these very same companies that are particularly susceptible to negative changes in investment incentives from a poorly-crafted follow-on biologics regime.*

This situation is very much unlike the situation involving the traditional small molecule pharmaceutical market at the time that the Hatch-Waxman Act created a generic drug pathway in 1984 – a market that was dominated by mature and profitable companies with substantial revenues to reinvest in pharmaceutical R&D. Thus, the risk of driving research investment out of the industry, and quite possibly out of the United States, is substantial if a follow-on biologics approval pathway does not contain sufficient incentives for continued innovation.

In order to ensure such innovation, BIO believes that a 14-year period of data exclusivity should be granted to biologics under a follow-on biologics regime. For a fuller discussion of the data supporting this position, see our response to the previous questions and please visit the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.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.**

BIO has not estimated a specific savings number. However, we believe that a framework developed by Henry Grabowski and the Analysis Group can help to inform this question.[29]

The paper contends that:

- The magnitude of the federal budgetary impact of proposed legislation is highly uncertain, as is the speed with which cost savings will be realized.
- Estimates of federal savings are very sensitive not only to the specific legislative language that emerges, but also to a range of critical assumptions about scientific, regulatory, and clinical issues, the nature of competition in markets for specific

[28] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

[29] Grabowski, Henry, *et al*. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf

biologics, as well as future intellectual property protection, and related litigation and the development of case law.

- All of these factors are highly uncertain, and any one of them could have a substantial impact on the magnitude of potential federal savings and the speed with which they are realized.
- As a result, best available evidence and straightforward economic analysis indicates that cost savings are likely to lie at or below the lower end of the range of estimates currently before Congress (e.g., $3.6 billion over ten years – AvalereHealth).[30]

The paper also notes that aggregate cost savings will reflect the impact of an expedited approval process on both prices and utilization of each affected reference biologic product. While there is considerable heterogeneity among these innovator biologics, the paper identifies a number of critical factors that will drive these market outcomes:

- The timing of patent expiry for these products, the nature of their intellectual property protection (more complex and more uncertain than for traditional small molecule drugs), and related issues (assumed to permit entry of follow-on biologics by 2013 to 2017 for the largest categories of federal spending on biologics approved under the Public Health Service Act)
- The time required to develop an FDA regulatory scheme, testing requirements, or product-class guidelines following passage of any legislation
- The time required for manufacturers to obtain regulatory approval (three to five years for pre-clinical and clinical testing, and one-and-a-half to two years for FDA review and approval) and to bring manufacturing capacity on-line (four to six years, likely developed concurrently with product development schedule)
- The evolution of utilization of currently approved biologics, driven by:
    - Demographics, disease incidence, medical practice, and regulatory and reimbursement practice
    - The pace and extent of uptake of next generation patent-protected products in markets where follow-on biologics have entered (limiting longer-term uptake of follow-on biologics in markets with unmet medical need)
- The nature of the competitive model in markets for biologics that experience entry by follow-on biologics (likely to be driven by the marketing of branded, proprietary products rather than the "commodity" competition based on price alone seen among generic small molecule generic drugs), and its effect on:
    - The pace and extent of uptake of follow-on products for currently marketed branded products (likely slower and less extensive than for many small-molecule drugs, or 10 to 45% follow-on product share)
    - The price impact of entry by follow-on products (limited discounts of 10 to 30% off brand, due to fewer likely market entrants than in generic drug market, among other factors)

[30] The Avalere Health study is available at:
http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf

Though outcomes are highly uncertain, budget savings are likely to be much smaller than suggested by some advocates. Therefore, the paper also urges a cautious approach in interpreting estimates of the federal budgetary impact of any regulatory framework for expedited review and approval of follow-on biologics.

For more detailed information, the study can be found at:
http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf

In addition, BIO has critiqued two studies (PCMA and Express Scripts) that claimed large savings from a follow-on biologics pathway. The studies overestimated the savings due to, among other factors:

- Aggressive assumptions on interchangeability
- Timing when savings would begin to accrue
- Mathematical errors

The critique may be found at: http://www.bio.org/healthcare/followon/20070222.pdf

A more recent study by Sonecon, which also suggested large savings, suffers from many of the same issues as the studies by PCMA and Express Scripts. Further, it contains a methodological error that results in an overestimate of savings of at least 110%.

The above discussion focuses on the short term. In the long run, the savings estimates are more difficult to make and depend on a number of factors such as scientific advancement.

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 is best answered by individual agencies and companies that received the Committee's letter. However, a study by Milliman, an international actuarial consulting company, has found that the "costs of innovative therapies will generally not create a large cost burden relative to other costs for private healthcare payers by 2011."[31] Whereas in 2006 biologics accounted for 5% of total private healthcare payers' costs on average, in 2011 biologics will account for 6% of total costs on average.[32] The study further found that "private payers can generally make minor changes in their benefit designs that will assure the affordability of innovative therapies for their members."[33]

[31] Pyenson, Bruce and Catherine Murphy-Barron. "Realizing the Value of FDA-Approved Therapies." Milliman, Inc. March 31, 2007.

[32] Ibid. It should be noted that biologics account for only 1.8% of overall U.S. healthcare spending.

[33] Ibid.

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

A well-designed follow-on biologics pathway that ensures patient safety and that provides sufficient incentives for innovation (that is, 14 years of data exclusivity) will have a positive effect on U.S. economic competitiveness and leadership. However, a poorly-designed follow-on biologics pathway that reduces incentives for biotechnology innovation would disproportionately harm the United States, and undermine U.S. leadership in strengthening the protection of intellectual property rights around the world.

Because the U.S. leads the world in biotechnology innovation, the impact of reduced investment in this area will be particularly acute here in the U.S. The latest data from Burrill & Company show that the U.S. continues to dominate the biopharmaceutical market, whether the measure is sales, R&D, employees or public companies:

US, European, Canadian, Japanese, Canadian, and Australian Biotech: Global Activity Measures (2005, U.S. dollars)

	U.S.	Europe	Japan*	Canada	Australia
Sales/Revenue	$71.5 B	$7.5 B	$0.82 B	$1.7 B	$1.0 B
Annual R&D	$18.5 B	$4.2 B	-	$0.6 B	$0.1 B
# of Companies	1,473	1,878	464	470	226
# of public companies	363	96	22	81	58
# of employees	146,100	32,470	4,171	7,440	6,393

*Japan – public companies only

The U.S.'s per capita biotech R&D expenditures are 574% higher than the European Union's (EU) per capita biotech R&D expenditures.[34] It also should be noted that:[35]

- The biotechnology industry's U.S. trade surplus grew from $593 million in 2000 to $1.8 billion in 2004 – an increase of almost 200%. Over the same period of time, overall U.S. trade in advanced-technology products decreased by more than 200% -- going from a net surplus to a net deficit.
- The biotechnology industry's U.S. exports grew from $1.7 billion in 2000 to $3.7 billion in 2004 – an increase of more than 100%.
- Between 2000 and 2004, U.S. jobs in the biopharmaceutical industry rose by 8.3%.
- The biopharmaceutical industry expands U.S. gross domestic product by at least $27 billion annually, on a permanent basis, for every one-time R&D investment of $15 billion. In 2005 alone, the U.S. biotechnology industry invested nearly $20 billion in R&D.

[34] R&D figures are from Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007. Population figures estimated as of July 2006.

[35] See URL: http://www.nsf.gov/statistics/seind06/c6/tt06-03.htm -- last accessed on February 1, 2008.

Thus, a follow-on biologics pathway that does not preserve the necessary incentives for continued biotechnology innovation would disproportionately and negatively affect the United States, the world leader in biotechnology innovation, and would drive investment towards less risky ventures, including those outside of the U.S.

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?

Patents are a critical element of biotechnology innovation. It is the strength and predictability of patent protections – along with substantial data exclusivity in any follow-on biologics approval pathway – that will entice investors to finance high-risk biotech endeavors. The development of a biopharmaceutical can take decades and hundreds of millions of dollars of private sector investment. And even with all of this effort, there is no certainty that a product will be commercially viable. Patents on biotech inventions, along with substantial data exclusivity in any follow-on biologics regime, reassure investors and potential partners that their investment in a biotech endeavor can be recouped down the road.

Any legislation that is perceived to undermine patent protections – such as a follow-on biologics regime based on similarity rather than sameness without alternative methods of protection such as substantial data exclusivity – will likely have a stifling effect on innovative biotech R&D. If a company does not have adequate time to recoup its investment (on average $1.2 billion to bring a biologic to market[36]), it will not engage in the research and development of future products. This reduction in investment also will be detrimental to American universities as less of their cutting-edge research and fewer of their technologies will be licensed because companies will not be able to recoup the R&D investment necessary to take a licensed technology from the laboratory to the marketplace. Investors will turn to other less risky ventures, and cutting-edge research (including the substantial public investment in basic research through the National Institutes of Health) will sit on laboratory shelves, as it often did prior to the Bayh-Dole Act and the Hatch-Waxman Act patent term restoration provisions. Society as a whole will suffer, as fewer cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions are developed.

For additional information, please see our answer to Question # 7 under the "Incentives/Exclusivity/Investment" section above.

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?

[36] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

If a follow-on biologics pathway were created without sufficient incentives for continued biomedical innovation, future research and development of innovative products would decline significantly. Please see our answer to Question # 7 under the "Incentives/Exclusivity/Investment" section above for more details.

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.?**

As we note above (please see our answer to Question # 5 in the "Regulatory/ Administrative" section of this document), it is very important that FDA provide guidance prior to the approval of follow-on products, which are an entirely new type of product (i.e., neither innovative nor generic). Because of the wide variety among types of biologics, it is essential that such guidance be specific to a particular product or product group.

The guidance development process, which includes the opportunity for public input, will have several important benefits. First, the provision of such guidance would provide for transparency with respect to agency decision-making, and such transparency is extremely important to public confidence in the safety of follow-on products. Second, the availability of such guidance will facilitate the development of follow-on biologics and, by providing an added degree of regulatory predictability, will likely encourage the entrance of more follow-on manufacturers to the market. Third, the opportunity for public input will allow innovators to contribute specific information gained from their lengthy experience in biologics manufacturing. Fourth, it would permit physicians, academics, and patients to provide valuable insights and data on the innovator product that might be relevant to the approval of follow-on products.

Therefore, we support the approach taken by the European Medicines Agency (EMEA), the European equivalent to the FDA, in developing guidance documents. EMEA pursued a science-based, transparent and open process. First, the European Union established basic principles for all biosimilars. EMEA then drafted and sought public comment on concept papers and broad guidelines that address quality and nonclinical/clinical issues separately. This was followed by more specific guidelines, which provide testing recommendations on a product-group-by-product-group basis. This transparent process included a public scientific workshop in which all parties were invited to offer input.[37]

A requirement for public proceedings on guidance documents need not delay consideration of follow-on biologics. In most cases, the European Union has completed product-group-specific guidance in 12-18 months. While FDA must conduct its own

[37] See Hearing Before the Energy and Commerce Subcommittee of Health, 110th Cong. (May 3, 2007), Statement by David Schenkein, M.D., vice president of Clinical Hematology/Oncology for Genentech.

guidance development process, it will have the benefit of what has been and can be learned from the European Union and, in some cases, this may allow FDA to complete guidance in a shorter time. Furthermore, we note that following passage of follow-on biologics legislation, there are administrative processes FDA will have to put in place prior to approval of follow-on biologics; these will be separate from any guidance requirement. A guidance requirement would run concurrently with the establishment of these processes and thus would not create any additional delay.

2. **Legislation passed by the European Parliament encourages innovation by providing 10 years of market exclusivity, extendable to 11 years for select new indications of use, for innovator biologics, thereby preventing the introduction of FOBs during that period. Should the U.S. be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?**

As we state in our answers in the "Incentives/Exclusivity/Investment" section above, a 14-year period of data exclusivity is necessary to avoid undermining incentives for the development of innovative biologics. And for the reasons explained more fully in response to the subsequent question below, anything less would jeopardize the United States' leadership role in producing innovative biotechnology medicines for the patients who need them.

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?**

If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, the result will be substantially less investment in biotech innovation. Because the U.S. leads the world in this area, the impact of reduced investment will be particularly acute here in the United States.

The latest data from Burrill & Company show that the U.S. continues to dominate the biopharmaceutical market, whether the measure is sales, R&D, employees or public companies:

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Thus, a follow-on biologics pathway that does not preserve the necessary incentives for innovation (that is, 14 years of data exclusivity) would disproportionately and negatively affect the United States, the world leader in biotechnology innovation, and would drive investment towards less risky ventures, including those outside of the U.S.

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?**

Because the legal, regulatory, and economic landscape for biotechnology is different in Europe versus United States, the pathway for approval of follow-on biologics (biosimilars) also will differ. However, BIO strongly supports a number of features of the European system, which can serve as a model for U.S. consideration.

With respect to substitutability, the European Medicines Agency (EMEA) and certain member states of the European Union have recognized the fundamental differences between drugs and biologics. Recently, the EMEA issued a statement that "[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional." BIO believes that, consistent with the policies of EMEA and many European countries, patients should not be dispensed follow-on biologics unless expressly prescribed by a physician.

[38] R&D figures are from Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007. Population figures estimated as of July 2006.

[39] See URL: http://www.nsf.gov/statistics/seind06/c6/tt06-03.htm -- last accessed on February 1, 2008.

With respect to the requirement for clinical trials, EMEA's product-group-specific guidelines to date make it clear that the agency will require clinical data, for example with respect to immunogenicity, in every case. In addition, these guidelines require extensive manufacturing data and preclinical studies (toxicology, PK/PD, etc). Finally, EMEA has clear authority to require post-market testing for a follow-on biologic.

Concerning naming, EMEA has clarified that "the name, appearance and packaging of a biosimilar medicine differ to those of the biological reference medicine" (http://www.emea.europa.eu/pdfs/human/pcwp/7456206en.pdf).

Finally, and as we note in our answer to Question # 1 in this section, EMEA has taken a science-based, transparent, and open approach to the development of product-group-specific guidance for biosimilars.

5. **FOBs are now approved in Europe, and FDA has approved a number of follow-on protein products under the FFDCA. Have these shown any problems with respect to safety or efficacy? In what ways are these different from any safety problems seen with brand products?**

The Food and Drug Administration and individual manufacturers are best positioned to provide answers to these questions.