Barr Pharmaceuticals, Inc.

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May 2, 2008

The Honorable Frank Pallone, Jr.
Chairman, Subcommittee on Health,
Committee on Energy and Commerce
237 Cannon Building
Washington, D.C. 20515

The Honorable Nathan Deal
Ranking Member, Subcommittee on Health,
Committee on Energy and Commerce
2133 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Pallone and Ranking Member Deal:

On behalf of Barr Pharmaceuticals, Inc., as well as the millions of American consumers we serve each year, we thank you both for your continued interest in legislation to establish an effective and workable generic biologic approval pathway. Given the considerable importance of such legislation to all Americans, I want to thank you for the opportunity to respond to the questions you propounded on April 3, 2008.

After reviewing Barr's responses, should you or any other Member of the Committee have any questions or require any additional information, please do not hesitate to ask. Barr looks forward to continuing to work with you and others in Congress on this important issue.

Sincerely,

Bruce L. Downey
Chairman and CEO, Barr Pharmaceuticals, Inc.

Enclosure

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

The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

Written Responses From Barr Pharmaceuticals, Inc.

Barr Pharmaceuticals, Inc. submits the following written responses to the questions propounded by Chairman Pallone and Ranking Member Deal on April 3, 2008:

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?*

   Response: In simple terms, "immunogenicity" is the ability of a particular substance to provoke an immune response in the body. Unlike traditional small molecule drugs, biologics present immunogenicity concerns because of the size of the drug molecule. Generally speaking, larger and more complex molecules present more immunogenicity risks than smaller, less complex molecules.

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?*

   Response: Congress long ago gave FDA the authority to decide what types of studies are required for the approval of new biological drug products. Congress should give FDA the same authority with respect to generic versions of these products. More specifically, FDA must be given the authority to determine on a case-by-case basis whether immunogenicity studies are needed for generic biologics and, if studies are needed, the discretion to decide what types of studies should be conducted. Indeed, FDA should have the authority to determine what types of studies in general are necessary and appropriate when evaluating generic biologic applications – again, just as FDA has when evaluating new biologic products. FDA has decades of experience reviewing and approving biological drug products and should be permitted to utilize that expertise when approving generic versions of these products. Mandatory study requirements imposed by Congress run, among other things, the risk of requiring unethical, duplicative human drug testing. Indeed, as one biotech representative recently testified before this Committee, it "is important that Congress not seek to create a one-size-fits-all testing requirement, to ensure purity and identity, because a one-size-fits-all approach will not work for all safe, pure and potent biologics. Rather FDA must have the responsibility and discretion to ensure appropriate testing based on each particular product . . . ." (Source: James C Greenwood, Biotechnology Industry Association, Testimony, May 1, 2008, House Energy and Commerce Subcommittee on Health Hearing).

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?

Response: FDA currently has the authority to determine whether immunogenicity testing for manufacturing changes is necessary and, if so, what type of testing should be required. We see no reason to change this policy for branded companies, and no reason to adopt a different framework – one involving Congressionally-mandated requirements – when it comes to FDA's review of generic applications.

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?*

Response: When based on sound science principles, satisfying the approval criteria with respect to one indication should result in FDA approval of all other indications sharing the same mechanism(s) of action. Generic biologics legislation must not mandate the indications for which an applicant must seek approval. Proposals, such as H.R. 5629, that would require generic applicants to seek approval for all indications of use for which the brand has received approval have no scientific justification. Rather, such proposals would only improperly delay (if not prevent) the introduction of safe, effective and far more affordable generic medicines.

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?*

Response: FDA should have the authority to require risk evaluation and mitigation strategies (or REMS) under the Federal Food, Drug, and Cosmetic Act ("FFDCA") vis-à-vis generic biologic products, just as the Agency has with respect to branded biological products approved under 42 U.S.C. § 262(a), and the REMS required for generic biologics should be no greater than that required for the corresponding brand biologic 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?*

Response: Non-interchangeable generic biologics should not be given different non-proprietary names. Among other things, there likely will come a time when such products will be deemed interchangeable, and the previous, different name could be confusing. Furthermore, in September 2006, FDA supported this position when it

announced that a generic biologic should not be given different non-proprietary names from its reference product. (*See* http://www.fda.gov/ cder/news/biosimilars.htm). As FDA explained, given the drug approval and prescribing laws in the United States, different names are not necessary to ensure public health and safety. The reason the brand industry seeks different non-proprietary names is because they hope to thwart generic substitution. Specifically, they believe that different non-proprietary names will make substitution far more difficult. Any such statutory requirement would significantly reduce the savings that flow from an effective, science-based generic biologic approval pathway.

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?*

Response: For the vast majority of approved products, including small molecule drugs and large biologic drugs, the exact mechanism of action is not clearly elucidated. The clinical endpoint for each is, however, well-known and well-defined. Therefore, it is important that the reference product and generic product have the same clinical endpoint. To require a generic biologic to determine the mechanism of action when the same is unknown for the reference product would serve only to improperly delay (if not prevent) the introduction of safe, effective and far more affordable generic medicines, with no benefit to public health.

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?*

Response: As the brand industry well knows and has demonstrated, there can be considerable batch-to-batch variability with biological products, and manufacturing changes can add to that variability. Yet, FDA considers different batches of brand products to be interchangeable as long as appropriate manufacturing controls and specifications are in place. The same is true for batches produced after manufacturing changes, so long as the Agency's comparability guidelines are satisfied. This experience demonstrates, among other things, that a generic biologic does not have to be "identical" to the reference product in order to be considered interchangeable; that generic biologics should not be required to have different non-proprietary names; and that a generic biologic can safely be approved even if there is some variability between it and its reference product.

9. *Should human clinical trials be mandated by statute for all FOBs or should FDA be given discretion whether such trials are needed on a case-by-case basis? Would not requiring human clinical studies of FOBs result in these products having a more difficult time reaching market acceptance? Why or why not?*

Response: As discussed above, FDA must be given the authority to determine on a case-by-case basis what studies are needed for the approval of generic biologics, just as FDA current has the authority to decide what studies are needed for the approval of new, branded biological products. While it is likely that in the early years of a generic biologics program FDA would require human trials for most products, there will come a time in the future when, as FDA has recognized, human trials are not necessary to demonstrate safety and efficacy. As a result, mandatory, statutory study requirements imposed by Congress run, among other things, the risk of requiring unethical, duplicative human drug testing.

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?*

Response: The studies required for approval of protein products under section 505 of the FFDCA has run the gamut from small PK studies to large clinical efficacy studies. Insulin, human growth hormone, calcitonin, hyalurondase, and desmopressin are examples of protein products approved under section 505 of FFDCA.

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?*

Response: (a) We are not aware of any problems experienced with Omnitrope. (b) The NDA for Omnitrope included studies to support the use of the product in children and extensive analytical and characterization data. The sponsor did not conduct studies in the adult population. When FDA approved Omnitrope, the product was, however, labeled for both pediatric and adult use, as the Agency used its scientific expertise, knowledge of human growth hormone, and experience with other approved human growth hormones to extend the approved indication. Therefore, patients can be switched from Genotropin, the referenced product, to Omnitrope. (c) We do not have payer information on the product.

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?*

   Response: Section 505 of the FFDCA provides a regulatory pathway for the approval of generic versions of biological drug products approved under that Act. To the extent Congress considers moving the approval of such products to the PHSA, it must do so cautiously. First, Congress should protect the settled expectations of stakeholders by providing a sufficiently long period for submitting applications under the current statutory scheme. An immediate move would disrupt current R&D plans of companies preparing applications for generic versions of such products. Second, any transfer must not allow brand companies to take advantage of exclusivity given to branded products approved under the Public Health Service Act ("PHSA"). Biologic products approved under the FFDCA already have received the incentives and rewards that Congress gave to such products. There is no reason to delay the public's access to affordable generic medicines by giving FFDCA biological products any additional exclusivity that might be available to products approved under the PHSA simply because Congress moves such products from one statute to another.

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?*

   Response: FDA has developed a comparability protocol guidance that must be followed for changes to an approved biological product. To our knowledge, FDA has exercised appropriate discretion with respect to whether a change to an approved branded biological product requires a clinical trial. FDA has been doing so for well over a decade and, to date, we are unaware of any adverse impact on patient safety. Congress should continue to give FDA the discretion to decide what tests are necessary to approve biological products, both for new products and for generic versions of these medicines.

3. *What FDA office should review FOBs?*

   Response: The Office of Drug Evaluation, within the Office of New Drugs, reviewed and approved the reference product. The Office also should review and approve the generic product. This would allow the Agency to capitalize on the existing core competencies and internal expertise and experience.

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?*

Response: Not even BIO disputes that the science exists to create safe and effective generic biological products. Yet some of the generic biologics bills introduced in the House would establish scientifically-unjustified standards designed to make it almost impossible, if not entirely impossible, to obtain approval for generic products. More important than the label given to the approval standard are the requirements embodied by the standard. A generic product should be approved if the applicant presents data establishing the absence of clinically meaningful differences between the proposed product and the brand reference product in terms of safety, purity, and potency. In deciding whether this standard is met, it is critical that Congress allow FDA to utilize its expertise to determine what data is needed.

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?*

Response: The law does not require FDA to issue guidances or regulations prior to approving branded biological products (or traditional drug products for that matter). That is, for products with which the Agency has no prior experience whatsoever, Congress has not required FDA to engage in a public guidance process. FDA therefore should not be required to issue guidances or promulgate regulations before accepting, reviewing, or acting on generic applications. As is the case for brand products, the use of guidances or regulations for generic products should be left entirely to FDA's discretion.

Moreover, the history of guidance and regulation issuance suggests that such a requirement almost certainly would delay the approval of generic biologics for many years, without any benefit to the public health. It can, for example, take FDA years to begin the guidance process, and once it does begin the process, it can take the Agency several more years to issue a draft guidance. A review of FDA's guidance webpage shows several draft guidances issued as far back as 1999 – drafts for which FDA has not yet issued (and may never issue) final documents. As of the end of February 2008, FDA's guidance webpage listed *over 100 draft guidances* currently issued by FDA, excluding draft International Conference on Harmonisation guidance documents. Conducting formal notice-and-comment rulemaking can take even longer than issuing a guidance. For example, Congress enacted Hatch-Waxman in 1984. FDA did not publish proposed regulations for ANDA approvals until 1989. The Agency adopted some final regulations in 1992, with others following in 1994 – more than *10 years after* enactment of that Act. At the end of the day, mandatory guidance proposals such as those found in H.R. 5629 or H.R. 1956 serve only to delay the introduction of safe and affordable generic versions of such products as EPO, which FDA approved back in 1989.

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?*

Response: Without specifics regarding the nature of the abbreviated approval pathway, we do not have enough information to provide a response to this inquiry.

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?*

   Response: The science currently exists to demonstrate that a generic biologic is interchangeable with the reference product. These assessments can be done today, as part of the development program to support the approval of a generic biologic product.

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

   Response: Depending on the size and complexity of the generic biologic, detailed physiochemical, structural, analytical and characterization data may be sufficient. In situations where additional data may be needed, clinical studies investigating the safety and efficacy of "switching" the reference product for the generic product can be conducted.

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.*

   Response: There is no scientific justification for requiring Congressional action prior to the approval of interchangeable generic products, and Congress should not statutorily bar FDA from making an interchangeability determination. Such an artificial limitation unnecessarily ties the Agency's hands, which harms industry, consumers and taxpayers. To be sure, the public will benefit from the introduction of "biosimilar"/"comparable" generic biologics, but consumers and taxpayers will see the most significant savings when interchangeable products come to market. FDA should, therefore, have the authority, based on sound science, to determine when an applicant has provided enough data to establish interchangeability with respect to a particular product.

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?*

   Response: As discussed in detail above, a mandatory guidance or regulation process prior to the submission or approval of generic biological products serves only to delay the public's access to safe and affordable medicines. If FDA believes that a notice-

and-comment rulemaking or a guidance process including public comment would be helpful, the Agency already has the authority to undertake such a process.

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?*

Response: If FDA deems one biologic interchangeable for another, then all health care providers and patients should feel comfortable with substitution by the pharmacist. This would be no different than FDA deeming two small molecule drugs interchangeable. Any potential risks from interchangeability would be a different clinical effect and an increased risk of immunogenicity. This, however, would be assessed by FDA prior to deeming the products interchangeable.

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

Response: As explained above, Hatch-Waxman has demonstrated that a financial benefit will flow from the introduction of "biosimilar"/"comparable" generic biologics, but consumers and taxpayers will see the most significant savings when interchangeable products come to market. The cost savings that will follow from increased competition brought by interchangeable generic products will be substantial, a topic discussed in more detail 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?*

Response: Branded drug products – both traditional and biologic – typically are protected by a broad range of patents that issue over time and thus provide years, if not decades, of patent protection. Generally, how far out after drug approval such patents extend can most accurately be answered for small molecule drugs because Hatch-Waxman requires brand companies to submit to FDA all patents claiming "the drug" or an approved method of using "the drug." 21 U.S.C. § 355(b). Since a similar list does not exist for biologics approved under the PHSA, it is more difficult to determine which patents the brand company believes covers its commercial product and thus is more difficult to determine the effective patent term for such drug products.

Hatch-Waxman permits brand companies to list in the Orange Book only a small subset of the patents that companies own or license. Process patents, intermediate patents, and unapproved use patents, for example, cannot be listed. Yet, even a quick review of FDA's Orange Book shows that brand companies routinely obtain (either as the assignee or licensee) and list multiple patents extending years beyond FDA approval of

the drug product. When "unlistable" patents are included, the scope of protection is expanded considerably. For example, with respect to one traditional product of which Barr is aware, the innovator company has obtained over 200 patents (some eligible for listing in FDA's Orange Book and some not), which translates into nearly four decades of patent protection for that drug. How long these patents, or any patent relating to a drug product, are "effective" at preventing generic competition depends on the subject matter claimed, as well as the validity and enforceability of those patents. But, to be sure, brand companies have patents relating to their drug products that extend many years beyond FDA approval.

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

Response: As an initial matter, brand biologics manufacturers already benefit from Hatch-Waxman's patent term restoration (or "PTE") provisions and they have done so since Congress enacted these provisions in 1984. But, of course, these companies have not been subject to generic competition, like traditional manufacturers have, as part of the balance Hatch-Waxman struck. Thus, the question becomes, are the Hatch-Waxman exclusivity periods a good model vis-à-vis generic biologics legislation. We believe that the brand companies should be required to demonstrate that an additional exclusivity period is necessary as an incentive to innovation before exclusivity is included in any legislation. If, however, Congress believes brand biologics makers need additional incentives to continue research and development, then the answer is "yes."

The past 20-plus years have conclusively demonstrated that Hatch-Waxman struck the right balance between innovation and increased generic access. Brand companies continue to develop new and innovative products, while consumers obtain faster access to a wider range of affordable generic products, which saves literally billions of dollars a year. Consequently, Hatch-Waxman establishes the maximum number and length of the regulatory exclusivities that should be awarded to branded drug companies – whether traditional or biologic.

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?*

Response: Valid and enforceable patents protect biologic products from competition to the same extent that they protect traditional small molecule drugs. There simply is nothing about biological products that prevents companies from obtaining meaningful patent protection. Indeed, this fact is amply demonstrated by the number of times that biologic patents have been successfully asserted against other biologic makers in the brand vs. brand disputes that have been, and continue to be, litigated in the courts.

How traditional and biological products are claimed might be different, but, just like traditional drug makers, biologic companies get patents effectively covering, among other things, the compound itself; manufacturing processes; individual steps in the manufacturing process; various delivery devices; dosing regimens; and method of using the compound. Biological product patent applications also might take longer to prepare and prosecute, but again, this does not prevent companies from obtaining meaningful patent protection. Indeed, PhRMA and BIO were extremely vocal during Congress' patent reform discussions because, they said, biologic patents are so valuable and important to their members. Finally, this question talks in terms of an applicant "only" having to establish that the generic product is highly similar to the brand reference product, as if this is an insubstantial burden or a low standard. It is not. Having to present data establishing a lack of clinically-meaningful differences between the proposed product and the brand reference product in terms of safety, purity, and potency, as several bills define the concept of "highly similar," will take considerable resources and expertise.

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?*

Response: An efficient patent dispute resolution mechanism will be an essential component to any effective generic biologics legislation. By way of background, generic companies, by definition, sell their products for less – most often far less – than the corresponding branded drug product. As a result, generic companies must have patent certainty prior to marketing. Without it, a product launch could subject the company to massive damages that threaten its very existence. The required certainty for some patents, but by no means all patents, will come through litigation. The most efficient and effective generic biologics legislation will allow the generic company to decide which, if any, patents should be litigated *before* product launch.

This is not to say that a patent holder (whether the brand itself or a third-party) should be foreclosed from bringing suit on any patent that it in good faith believes is infringed. Rather, it is a question of timing: Only certain patents should be litigated during the FDA review process before the generic biologics product is launched. Specifically, the only patents that should be litigated immediately, during the FDA review process, are those patents that would prevent the generic company from launching until questions of validity, enforceability or infringement are resolved. Litigation on all remaining patents would take place *after* the generic product actually enters the market. There are many reasons for this, not the least of which is the fact that the more patents involved in the litigation, the longer the litigation will take, and as a result, the longer the public will have to wait for the introduction of affordable generic biologics.

Equally as important, if a brand company refuses to participate in the patent process, as increasingly happens with small molecule applications under Hatch-Waxman, the generic company must be allowed to enter the market without risking potentially massive infringement damages. H.R. 1038 accomplishes this by limiting the remedies

available to patent holders that refuse to participate in the patent process. These provisions simply ensure compliance with clear-cut statutory obligations. The industry's experience with Hatch-Waxman has shown that some brand companies do not always comply with express and unambiguous statutory requirements when failing to do so provides a commercial benefit without penalty. Hatch-Waxman, for example, does not provide a penalty for failing to comply with the Orange Book listing requirements. Several brand companies routinely abused the FDA Orange Book patent listing process in order to delay ANDA approvals. FDA refused to enforce Hatch-Waxman's express patent listing requirements, and the courts refused to allow private companies to enforce those requirements. Consequently, when crafting effective generic biologics legislation, provisions ensuring compliance with the patent resolution mechanism are crucial.

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?*

Response: As previously discussed, to operate in any meaningful way, generic biologics legislation must include a patent dispute mechanism that provides expedited review for a select group of patents. Where one of those patents is owned by a third party, rather than the brand, the statute should include a mechanism for involving that third party in a way that does not delay the patent resolution process. Patent proposals like the one in H.R. 5629 will not bring about expeditious resolution and will only work to delay generic market entry.

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?*

Response: FDA's resources and expertise are best spent reviewing and approving drug applications, not administering a patent listing process similar to the one found in Hatch-Waxman. This is not to suggest that the Hatch-Waxman patent listing system should be changed or has not, in general, served its purpose. Rather, it reflects the fact that an alternative patent process for generic biologics could be more efficient, while eliminating any need for FDA involvement, which allows the Agency to focus on drug approvals and not patent issues.

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?*

Response: As an initial matter, it is important to note that the law currently provides branded biologic manufacturers with a multitude of financial incentives to develop new products, including:

Current Incentives Available To Brand Biologics Companies	
Patent Term Restoration	Compensates drug manufacturers for a maximum of 5 years of patent time lost while testing a product and awaiting government approval. *See* 35 U.S.C. § 156.
PTO Patent Restoration	If a patent's approval is delayed due to the fault of the PTO, gives drug manufacturers one day for every day over three years for review of patent. *See* 35 U.S.C. § 154(b)(1)(B).
Orphan Drug Exclusivity	Gives drug manufacturers 7 years of market exclusivity for drugs intended to treat rare diseases (affecting less than 200,000 people or where the cost of development cannot reasonably be recouped by U.S. sales). *See* 21 U.S.C. § 360cc.
Orphan Drug Tax Credits	Allows drug manufacturers to claim a tax credit equal to 50% of the cost of human clinical trials for drugs intended to treat rare diseases. *See* 26 U.S.C. § 45C.
General Business R & D Tax Credit	Allows drug manufacturers to claim 20% of their qualified spending in the U.S. above a base amount. *See* 26 U.S.C. § 41.
Puerto Rico Activity Tax Credit	Allows U.S. corporations to exempt 40% of their income from business operations they own in Puerto Rico, the Virgin Islands, or other U.S. Territories. *See* 26 U.S.C. § 936.
Foreign Tax Credit	Allows U.S. corporations paying taxes to foreign governments to claim a limited tax credit for those payments. *See* 26 U.S.C. § 901
Uruguay Rounds Agreement Act Patent Term Restoration	Gives drug companies a 20 year patent from the date that the patent was filed (rather than 17 years from patent issuance). *See* 35 U.S.C. § 154(a)(2).

To the extent that brand companies believe that additional incentives are necessary, they should come forward with actual evidence supporting this request. So far, brand companies have made demands for additional incentives founded only on self-serving speculation.

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?*

Response: To our knowledge, an objective assessment to determine what, if any, exclusivity is necessary to ensure a robust brand biologics industry has not been conducted. The Congressional Research Service has, however, concluded that Hatch-Waxman "has not deterred the search for and development of new [traditional, small molecule] drugs." (CRS Report for Congress: Patent Law and Its Application to the Pharmaceutical Industry: An Explanation of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act") at 36 (Dec. 18, 2000)). Hatch-Waxman, of course, provides 5 years of exclusivity for new chemical entities, and 3 years of marketing exclusivity for certain changes to previously-approved drug products. *See* 21 U.S.C. § 355(j).

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

Response: This question assumes that any exclusivity should be awarded for modifications to previously approved drugs. That said, as noted above, the exclusivity system enacted by Hatch-Waxman strikes an appropriate balance between incentivizing innovation and increasing access to affordable generic medicines. Hatch-Waxman provides 3 years of marketing exclusivity for new indications of use for previously-approved drugs and for modified dosage forms of such products, when the statutory criteria are satisfied. *See* 21 U.S.C. § 355(j).

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

Response: Regulatory exclusivity is absolute in the sense that a generic company generally cannot effectively challenge exclusivity periods in court or design around them in order to get an earlier approval. They prevent generic competition even if the brand company has no patents whatsoever protecting its drug product. In this important respect, regulatory exclusivity differs from patent protection. Patents can be challenged in court and, in some instances, designed around.

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

Response: We have seen no actual evidence demonstrating that branded biologic companies need any additional incentives, let alone greater incentives than traditional drug companies receive under Hatch-Waxman. Indeed, if anything, biologics companies likely need fewer incentives because they will not experience the same extent of generic competition that traditional drug makers face. For example, unlike companies under Hatch-Waxman, biologics makers will have fewer generic competitors. (*See, e.g.*, October 22, 2007 *Investor's Business Daily* ("Pfizer also has figured out that biologics can be more profitable than pills . . . . A drug firm might get 10 years of patent protection on conventional, chemical-based drugs. Biologics, which are made from human or

animal-based proteins, can keep a hold on their markets longer because production is too complicated and expensive for most generic manufacturers. 'Instead of having a pill for 10 years, biopharma companies can keep a biotech drug forever'.")).

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

Response: Patents protect novel and innovative products, and thus provide the incentive needed to develop new drug products. That is, patents allow brand companies to block generic competition so long as they come up with new products that can be patented. This benefits consumers who have more new medicines available to them. Regulatory exclusivity, on the other hand, is absolute (even if there is nothing novel or innovative about the brand product) and thus does not provide any incentive for drug companies to investigate new products. In other words, patents spur new innovation because only new innovations are protected by patents and thus from competition. Regulatory exclusivity protects from competition without innovation so consumers and taxpayers pay more money, but receive fewer new drugs in return.

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?*

Response: We are not aware of any evidence that demonstrates, or even suggests, that continued research and innovation would be affected or that the patent system and other, existing exclusivities are not a sufficient incentive. As noted above, several financial incentives exist, including so-called "orphan drug exclusivity," which provide significant financial incentives for brand companies.

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.*

Response: We have not independently undertaken an analysis of the cost savings that an effective generic biologics bill would generate for consumers and taxpayers. Others have, however. For example, Citizens Against Government Waste (CAGW) in May 2007 released a report entitled "Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers." The report estimates that if Congress enacts an appropriate statutory framework to approve generic biologics, these drugs could save taxpayers and consumers *$43.2 billion between 2011 and 2020.* (*See* Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers, by Everett Ehrlich, PhD, Elizabeth L. Wright (May 2, 2007)). Express Scripts also conducted a study. According to that study,

an effective approval pathway would result in *$71 billion* in savings for the during the first 10 years. (*See* Potential Savings of Biogenerics in the United States (February 2007)). BIO has quibbled with the Express Scripts figure, but, at the end of the day, not even BIO disputes that an effective pathway will save billions of dollars each year.

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?*

Response: Barr has publicly acknowledged that it currently is pursuing a variety of generic biologics, including a generic version of Amgen's Neupogen® and a vaccine being developed for the U.S. Department of Defense. But the terms of any legislation that Congress enacts will determine in large part how much our company spends developing additional generic biologic products. If, for example, Congress enacts legislation establishing an unworkable approval pathway or unreasonably long brand exclusivity periods, companies simply cannot invest the significant monies needed to develop generic biologics. If, however, Congress enacts a workable and effective approval pathway, Barr and others will continue to make the investments needed to bring more affordable generic products to market.

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

Response: Creating an effective approval pathway for generic biologics will further enhance the U.S.'s economic competitiveness and leadership in the protection of intellectual property rights. Competition in the biologics area not only would enhance America's competitiveness, but would spur new innovation. This is, of course, precisely what happened when Congress enacted Hatch-Waxman in 1984 – it created a significant incentive for brand companies to create new products, rather than simply sit back and enjoy a never-ending stream of monopoly profits on old products.

More specifically, without competition, brand companies have little, if any, incentive to develop the new, truly innovative products that benefit patients. Rather than invest significantly in entirely new products and product lines (which carries financial risk), they can simply rely on the generous revenue stream that their ongoing monopolies on older products generate. But competition from generic products pressures brand companies to develop new products and improve existing ones to maintain profit margins. Consider, as one example, the development of traditional drug products to treat gastric ulcer disease. Brand companies developed H_2-receptor antagonists such as cimetidine (Tagamet®) and ranitidine (Zantac®) first to treat gastric ulcer disease, and then for the treatment of gastroesphageal reflux disease (GERD). These products, while protected by patents and Hatch-Waxman regulatory exclusivities, generated billions of dollars in sales. As generic companies began to develop competing versions, brand companies responded by developing the next class of treatment, proton pump inhibitors.

AstraZeneca's omeprazole (Prilosec®), once a multi-billion dollar product, is perhaps the most well known of these drugs. Many touted this new class of drugs as a more effective treatment for GERD. But as generic competition for omeprazole loomed, AstraZeneca developed a new product, esomeprazole (Nexium®). Patients taking esomeprazole reportedly experience better healing rates of esophageal erosions than patients taking omeprazole. We expect that brand companies will be looking for the next, improved GERD treatment as generic competition for esomprazole begins to take shape.

The fact is, the biologic drug industry may owe itself in part to generic competition. After Congress passed Hatch-Waxman in 1984, brand companies knew that they would face increased competition for sales of traditional small molecule drugs. Many began investing their resources in what was then a fledgling industry, developing biologic drug products. These investments brought about numerous new life-saving drugs, as well as significant advances in the technology needed to produce and characterize these drugs. Hundreds of additional products currently are in the pipeline. While these investments might eventually have been made, the competitive pressures that generics created provided the incentive for this research and development to be done sooner rather than later. The market dynamic created by generics thus benefits the U.S. (including U.S. consumers) in two important ways. First, generics provide the public with quality, lower-priced alternatives to brand name drugs, saving consumers and taxpayers billions of dollars a year while increasing access to those with restricted income. Second, generics provide the urgency for innovation, forcing brand companies to constantly strive for new and revolutionary treatments. And as brand companies develop new biologic products, they will obtain patents to protect them, which will further the U.S.'s leadership in intellectual property matters.

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?*

Response: Patients will benefit considerably from the enactment of an effective approval pathway for generic biologics. As discussed in detail above, competition in the biologics area would spur new innovation. Rather than rely on revenue from older products, the competition that flows from generic medicines would force brand companies to develop entirely new products and product lines. Thus, patients would benefit in at least two important respects from an effective generic biologics bill: (1) it provides them with access to far more affordable versions of existing biologics medicines; and (2) it provides them with access to entirely new medicines that might not have been pursued (or pursued as soon) but for generic competition on existing product lines.

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?*

Response: As discussed above, considerable incentives already exist, including patent term restorations and significant periods of market exclusivity for orphan drugs.

And, of course, biologics manufacturers and universities have long availed themselves of the considerable protections afforded by valid and enforceable patents. No one, including BIO, has come forward with actual evidence, as opposed to self-serving speculation, that additional incentives are needed to ensure continued research and development.

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.?*

Response: The EU regulatory system has been developed, and has evolved, to meet the legislative, cultural, medical and geographical framework mandated by the now 25-country European Union. The evolution of this process to allow for the approval of biosimilar products included the development of product-specific and regulatory requirement guidances. One objective of this process was to ensure transparency across the EU, which is not one country, but rather 25 different countries with different laws. We do not have a similar situation in the U.S., which eliminates the need for such a mandatory guidance process. In fact, given the U.S. regulatory framework, as discussed above, a mandatory guidance process would hinder the timely approval of safe and effective generic biologics.

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?*

Response: BIO often points to the exclusivity periods available in under the EU to justify its demands for 12 to 16 years of exclusivity in the United States. To be clear, the EU exclusivity periods provide no legitimate guide for how much exclusivity should be awarded in the United States. Longer exclusivity periods in the EU might be justified given the price controls that the EU imposes on branded drug products. As Congress is well aware, though, the United States does not impose any price controls on brand drug products, which explains why U.S. consumers and taxpayers pay far more than their EU counterparts for the same drug products. Yet another reason why Congress should not be guided by the EU exclusivity periods is the fact that EU and U.S. patent law differs significantly. The U.S. patent law allows companies to obtain much broader protection—and thus a much broader ability to exclude generic competition—than the EU patent law.

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?*

Response: Adopting substantially shorter exclusivity periods than those available in the EU will not harm U.S. competitiveness. As explained directly above, U.S. law

already gives brand companies considerable advantages not available in the EU, including the ability to charge U.S. consumers and taxpayers far more than they can charge consumers in the EU for precisely the same drug products. At the end of the day, comparing the EU incentive system to the U.S. system simply is a pointless apples-to-oranges comparison that does not meaningfully advance the dialogue on this important issue.

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?*

Response: The current EU model is suitable for the EU, as it provides a pathway for biosimilars to be approved and for EU patients to have access to life-saving biosimilar products at a reduced cost. The advantage of the EU regulatory model is it has been validated and shown to work in the European Union. The disadvantage of the EU model is that it is neither portable nor transposable; meaning it cannot be simply copied and implemented in a country like the U.S.

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?*

Response: We are not aware of any safety or efficacy issues associated with these products.