GPhA Response to
House Energy and Commerce Committee
Questionnaire on Biogenerics

Science/Safety

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

Immunogenicity is the ability of a substance to stimulate the body's immune response, which usually means the generation of antibodies that are specific to the substance. The generation of antibodies to foreign substances, such as bacteria, is a normal response in keeping people healthy. People routinely make antibodies to many different substances and experience no negative effects.

Sometimes therapeutic biologics can cause patients to develop antibodies to the biologic protein. In many instances these antibodies are transient and patients continue to receive the biologic with no impact on safety or efficacy. Most antibodies to biologics are binding antibodies, which means they bind to the biologic, but do not neutralize its therapeutic activity. The development of immunogenicity typically would not be a reason to discontinue treatment with a biological product unless there is reason to believe that the antibodies have rendered the biologic ineffective. This situation is very rare.

Immunogenicity is not a unique issue for biologic products. Many drugs are known to cause immunogenicity in humans (e.g., penicillin). If we looked closely enough, it is likely that most all injected drugs cause a perturbation of the immune system.

Immunogenicity itself is not a risk or a safety issue because most antibodies do not affect safety or efficacy. In very rare instances a potential risk to the patient is the development of antibodies to the biologic that neutralizes an endogenous protein. This is extremely rare and has only been observed with one approved biologic (Eprex) in 25 years.

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?

Science is best left in the hands of scientists. The requirement for immunogenicity testing should be at the discretion of the FDA. The need for testing of a biogeneric, including immunogenicity studies, should be decided by FDA on a case-by-case basis based on the latest scientific knowledge.

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

FDA has appropriately exercised its discretion and used flexibility in deciding whether to require immunogenicity testing for manufacturing changes. Like biogenerics, immunogenicity testing after manufacturing changes should not be mandated, but decided on a case-by-case basis. Continuing to give FDA the discretion on the need for immunogenicity testing after manufacturing changes allows for flexibility in using new technology, such as more precise analytical technology and improvements in clinical assessments. The bottom line is that FDA should exercise its discretion whether to require immunogenicity testing for manufacturing changes.

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?

There is a long history in this regard for traditional drugs. For ANDAs, it is not necessary to provide evidence of safety and effectiveness for each indication. There is no reason to treat biologics differently. GPhA is unaware of any example where one protein had activity in an indication while another comparable protein did not.

When two biological products are declared comparable, they have been determined to have comparable structure and biologic activity. Judging the safety and efficacy of biogenerics to the reference product does not need to include replication of all safety and efficacy studies in all indications. Sponsors of biogenerics should not be required to unnecessarily duplicate numerous clinical trials in different indications, since demonstrating comparability of biologic structure and effects illustrates comparability across the entire range of clinical indications for which the reference biologic has been shown to be safe and effective.

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?

FDA has the authority to request post-marketing studies for any product in order to address issues of safety and efficacy. Since safety considerations are always paramount, FDA should have the authority to address safety of the biogeneric in the same manner as set forth under the Food and Drug Administration Amendments Act of 2007. Requirements for post-marketing studies for biogenerics should rely upon the usual standards FDA sets for products it regulates, and depend entirely on the amount of available data that exist on a particular parameter and the need (if it exists at all) for

more data to further characterize this parameter. The need and requirements for follow-up safety studies for biogenerics should be similar to, and in no way greater than, the standard for reference brand biologics.

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?

No. There should be <u>no</u> statutory requirement for separate and distinct names for biogenerics when FDA determines that there is convincing scientific data that demonstrates that the biogeneric has similar molecular composition compared to the reference product. This argument has been pushed aggressively by the brand industry across the globe. And FDA has rejected this argument as has the World Health Organization (WHO). Indeed, in a Sept. 1, 2006 paper on this topic, FDA did not believe that a unique non-proprietary name should be assigned. Different names simply result in confusion among doctors and other health care practitioners and patients.

It is important to recognize the intended use of non-proprietary names. The non-proprietary name, or international non-proprietary name (INN), is not intended to indicate interchangeability. Rather, the INN is a cataloging system intended to identify products with the same active ingredient. The INN system has been used for decades to provide health care professionals around the world with a consistent mechanism for communicating about the drug. In the U.S. there are many traditional small molecule drug products that have the same INN, but are not interchangeable. In the September 1, 2006 paper on this topic, FDA stated that it does not believe that a unique INN should be assigned based on when molecular characteristics and pharmacological class of the active ingredient are deemed to be comparable.

What should the standard be for interchangeable FOBs?

Based on molecular characteristics and other scientific evaluations, comparability comparisons have been used for over a decade by brand companies to make changes to products after approval. These comparability studies typically are based on an evaluation of molecular characteristics and rarely require human clinical studies.

Therefore, FDA has already established a scientific pathway and interchangeability should be determined on a case-by-case basis considering all critical aspects of the product and the comparability data in making the determination.

What are the advantages and disadvantages of requiring different non-proprietary names, including any affect on patient safety?

Advantages: None.

Disadvantages: Assignment of different names for biogenerics that are deemed to be comparable by FDA will result in multiple names for products that are clearly the same in molecular properties, and have the same safety and efficacy profile. The confusion caused by such a naming strategy will result in a presumption of difference by patients, payers and physicians. Acceptance of biogenerics will be greatly diminished resulting in monopoly-like market conditions for decades and increased health care costs.

The proponents of unique nonproprietary names for each biogeneric are attempting to delay, if not prevent, loss of market share to biogenerics. Assigning a different nonproprietary name to a comparable biogeneric very well could automatically preclude substitution in all 50 states, significantly delaying patient use of affordable biogenerics for a decade. This is, of course, one of the reasons why the brand industry is pushing so hard for such a requirement. The fact is, opponents have not been successful in persuading scientific bodies that comparable biogenerics should have different names, so they are now seeking to legislate this barrier.

What alternatives are available?

The solution is simple. If FDA determines that the biogeneric is comparable to the reference product (using the same scientific tools used for determining comparability of a brand product that undergoes a change), then the products are assigned the same INN.

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?

Many drugs and biologics have been approved without knowing the actual mechanism of action. With some brand biologics the mechanism of action is thought to be known, but for many other brand biologics it is not known.

FDA approval has been dependent on clinical results from trials that demonstrate safety and efficacy. Many safe and effective products would be delayed significantly and maybe indefinitely if the mechanism of action needed to be defined before approval and patients would have been denied access to important and potentially life saving drugs and biologics. Thus, it would be a deviation from long-standing FDA policy to require any company – let along the generic company – to have to determine the mechanism of action before approval. Indeed, we see no scientific justification for the biogeneric to have to prove the mechanism of action where the brand company received approval without having done so.

Further, when the brand makes a change to an approved biologic, FDA does not require that the innovator demonstrate the mechanism of action for the 'changed'

product. Rather, FDA requires the data that it deems necessary to assure that such product has the same therapeutic effect as the original product.

With protein products, biologic structure dictates function and activity. Before approval sponsors would typically demonstrate that a biogeneric would have acceptably comparable chemical and physical attributes that are important to the biological effect as the brand product. It might also be expected that a biogeneric would perform bioassays, in vitro tests and in animal model as necessary on a case-by-case basis. The chemical, physical, biological, and pharmacological characterization of a biogeneric ensures that it will have the same safety and efficacy in humans as does the brand product.

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?

It is known and widely accepted that all biologic products have some degree of variability batch-to-batch. This could be minor microheterogeneity (variability) for some proteins, or in the case of glycosylated proteins, there could be variation in the ratio of various glycoforms. This variability is controlled by setting product release specifications that define a specific range of values for each of the many analytical tests used for every batch. Each batch of product must fall within the specified range for every test in order to be released and marketed. This is true of both biologics and traditional drug products. The specifications are reviewed by FDA before approval. The setting of specifications sets the allowable boundaries for the product and allows for minor variability that does not affect the safety or efficacy of the product.

It is also known that changes to the manufacturing process can result in minor product changes. For example, a change in manufacturing site, scale (batch size) or fermentation usually causes changes in the glycosylation of a glycoprotein. The significance of these differences could be evaluated in bioassays, in vitro studies, animal studies and human pharmacokinetics studies. The product could be deemed comparable (but not identical) to its predecessor. The amount and type of data needed is at the discretion of the FDA. Full clinical studies are rarely needed to address minor product changes. FDA's review and experience with manufacturing changes has relevance for biogenerics.

Further, minor product changes are accepted for a brand product after a manufacturing change if comparability is demonstrated with the previously marketed product as long as the brand product retains the same name and interchangeability. The same scientific principles apply to biogenerics.

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 trials should be determined at the discretion of FDA on a case-by-case basis. Human clinical trials should not be mandated by statute. As Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA stated at the March 26, 2007 Government Reform and Oversight Committee Hearing, requiring unnecessary human clinical studies would be unethical. FDA should be given discretion to determine whether clinical data for the approval of a biogeneric is warranted. FDA has stated that they have traditionally used a great deal of flexibility in the approval of many products. This flexibility was cited in an FDA publication "The FDA's assessment of follow-on protein products: a historical perspective" (Nature Reviews Drug Discovery AOP, published online 13 April 2007). In the approval of biogenerics, the need for clinical data will not be the same for every product or every application.

Would not requiring human clinical studies of FOBs result in these products having a more difficult time reaching market acceptance? Why or why not?

The regulatory requirements for approval are a separate issue from market acceptance. Market acceptance will face many challenges just as small molecule drugs did in the late 1980s and early 1990s. There will no doubt be many voices that will work to decrease market acceptance because of the advent of generic competition. These issues are, however, best kept distinctly apart from the scientific issues.

Clinical studies should be required when deemed necessary by FDA. Performing clinical studies that are unnecessary to determine safety and efficacy would be unethical. Clinical studies in and of themselves will not create automatic acceptance. Rather, relying on the expertise and the scientific determination by FDA will create a level of confidence in the healthcare and patient communities. Further, FDA is the recognized gold standard for reviewing and approving drugs. As reported by Dr. Janet Woodcock at the March 26, 2007 Government Reform and Oversight Committee Hearing, "We believe that our finding of interchangeability is our word. We are saying that, scientifically, we believe those products are interchangeable and we would not do that unless that were the case and it were substantiated with scientific data."

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

FDA has reported that a clinical study was required for a 505(b)(2) NDA for calcitonin while no clinical studies were required for a 505(b)(2) NDA for glucagon injection. It also should be pointed out that over the last decade, FDA has used a comparability approach to permit various types of changes (cell line, manufacturing site, new manufacturer, etc.) to innovator products. Biogenerics would be an extension of the comparability approach used by FDA and outlined in the June 2005 IHC Guidance for Industry Q5E Comparability of Biotechnological/Biological Products subject to Changes in Their Manufacturing Process.

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?

GPhA is not aware of any problems experienced with Omnitrope.

Based upon publicly available information, it is our understanding that the 505(b)(2) application for Omnitrope included studies to support the use of the product in children and extensive analytical and characterization data, but no studies in an adult population. However, when the Agency approved the product, it was labeled for both pediatric and adult use.

GPhA does not have access to the information needed to respond on the payer aspect of this question.

Regulatory/Administrative

1. Some believe Section 505 of the FFDCA provides a regulatory pathway for approval of biosimilars for reference products approved under Section 505. Should a newly created biosimilar regulatory approval process include all biologics approved under the FFDCA as well as those regulated under the Public Health Service Act?

GPhA believes that all products currently approved under section 505 of the FFDCA should continue to be regulated under that statute. A new pathway for biologics should apply to all products subject to the Public Health Service Act (PHSA).

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

The PHSA gives FDA extraordinary discretion in approving all products. For new innovative products with no previous history (other than limited clinical studies) of use in humans, FDA determines whether the product is safe and effective. The PHSA has very little prescriptive language, but rather relies on the expertise of FDA to determine the appropriate tests necessary for approval.

Every day, FDA makes critical safety and efficacy decisions for novel compounds never before used in humans based on broad statutory language. Some claim, however,

that FDA is <u>not</u> capable of making decisions on biogeneric products for which extensive data exists (e.g., physico-chemical comparability, marketing history, clinical data, etc.). That claim has no scientific justification. When a biogeneric becomes eligible for approval, FDA and industry typically will have had considerable real world experience with the reference product.

3. What FDA office should review FOBs?

Initially biogenerics should be reviewed by the CDER staff with current responsibilities for these products. In the future, they should be reviewed by the Office of Generic Drugs, although additional resources will be necessary.

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

FDA should have the discretion and authority to make determinations that the biogeneric is highly similar and will have the same clinical effect. A biogeneric should be approved if the applicant presents data establishing a lack of clinically-meaningful differences between proposed product and the reference product.

Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue and permit public comment on product-specific guidance before submission of applications? What are the advantages and disadvantages? How long will it take to put a regulatory framework in place, including new regulations and guidances for FOBs?

FDA should not be forced to propound a guidance or formal regulations prior to the submission or approval of a biogeneric application. A historical look is helpful. The Waxman-Hatch Amendments were passed in 1984. Proposed regulations were published in 1989 and final regulations were not published until 1992 and 1994. FDA has yet to publish regulations implementing the statutory changes reflected in the 2003 FDAMA. However, FDA accepted and approved thousands of ANDAs between 1984 and 1992 while waiting for regulations. It is clear that it will take years for FDA to publish and finalize implementing regulations. It would be bad public policy to delay the availability of safe, effective and affordable biogenerics for years while FDA works on implementing regulations.

Further, it typically takes two or more years for FDA to issue guidance. This process will be slowed by the voluminous comments to these guidances that are submitted by innovators seeking to delay the issuance of the final version. Guidances for human insulin and human growth hormone were initiated in the late 1990s and still have not been issued. More importantly, guidances are not necessary for industry or FDA to move forward with biogenerics.

By way of comparison, for a novel product, FDA will meet with a sponsor to agree on a product development plan. There are no guidances or public input on this process; yet, FDA approves dozens of safe and effective novel products each year based on sophisticated and innovative development plans that rely on current or sometimes groundbreaking science. Good science guides the process. Similarly, there should not be a mandatory guidance process for biogenerics.

Mandatory guidances or rule-making do nothing but delay biogenerics. While GPhA does not oppose issuance of FDA guidances or regulations when necessary, they should not be mandatory for FDA to accept and review biogeneric applications because they will result in unnecessary delays to access to safe, effective and affordable biogenerics.

5. 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?

GPhA supports user fees as one mechanism to fund a biogeneric program. The fee would be established based on the resource needs of the Agency and commensurate performance metrics for these applications.

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?

GPhA believes that interchangeability decisions are currently possible. As science and technology evolves, FDA will be able to make interchangeability decisions for an increasing number of products. The amount of testing will depend on the nature and complexity of the product. It would be impossible to determine a list of tests that would be suitable for every potential biogeneric. The types of testing would include assessment of chemical, physical and biological characteristics, but the nature of each category would vary greatly depending on the specific product because technology is constantly improving and the types of tests would be expected to evolve over time. Therefore, GPhA believes that interchangeability decisions are a reality for some biopharmaceuticals and the numbers will increase over the next five to ten years.

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

The testing platform for interchangeability will depend on the nature of the product and be determined on a case-by-case basis. For low complexity products, comparative characterization may be adequate. However, in most cases, comparative analytical characterization along with limited nonclinical and/or clinical evaluations will be

utilized to establish interchangeability. The 2005 ICH Guidance for Industry Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process and FDA's 1996 Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology – Derived Products outline general comparability approaches. At the end of the day, however, FDA must have the discretion to decide what types of tests and data are necessary to make an interchangeability determination.

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.

The statute must give FDA the authority to determine interchangeability as science permits. As previously stated, science is rapidly progressing. Imposing statutory requirements would ignore emerging technologies and limit FDA and industry to prescriptive requirements. Requirements should be established on a case-by-case basis.

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?

Product specific guidances, with public comment opportunities available, should not be required of the FDA before the submission of applications. Opponents of biogenerics will flood the FDA with comments in opposition to each guidance published by FDA – keeping biogenerics from patients for no legitimate scientific reason. This is, of course, precisely what we saw from Genentech, Pfizer, and others such as BIO when FDA attempted to issue biogeneric guidance documents. Waiting for public comment, the substantial review time by FDA staff to assess each and every comment, and the subsequent time for publishing guidance will take years.

FDA should rely upon its scientific expertise to make interchangeability decisions. FDA may wish to utilize guidances for some products, but the availability of guidances should not prevent submission and review of biogeneric applications.

Biogenerics legislation must give FDA the flexibility and discretion to shape the regulatory requirements necessary to determine safety and efficacy. Congress should not impose a statutory "check list" for the approval of biogenerics, but rather should allow the FDA to decide what studies are required and what procedures are appropriate, including whether product-specific guidances need to be issued. Under the PHSA, FDA has the authority to decide what requirements are applicable, even though the approval decision for a brand product is more complex than for a biogeneric. That same authority should apply to biogenerics, which will be sold only after the brand counterpart has been on the market. A product-specific guidance approach would create a double standard approval process that allows the brand manufacturer to potentially (and negatively) influence the approval criteria for a competing product.

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?

FDA will make interchangeability decisions only after its scientists have carefully evaluated the scientific information and determined that the biogeneric is therapeutically equivalent. If FDA approves a biogeneric, the public has the assurance of safety and efficacy. There is only one safety standard for all FDA approved products. There is not a lower standard for generic drugs or biogenerics. If FDA determines that two biologics are interchangeable, physicians, pharmacists, and patients should feel very comfortable with the use and substitution of one product for another.

The availability of biogenerics will provide lower cost alternatives to brand biologics, which are often extremely expensive (tens of thousands of dollars per year – up to $200,000 a year). Additionally, affordability is usually associated with better patient compliance and better compliance typically means a better medical response. Affordability also means that a greater number of patients will have access to the important clinical benefits that biologics represent.

In effect, FDA already makes interchangeability determinations. When a reference product makes certain changes after approval, FDA assesses the comparability data (analytical characterization along with any clinical data that might be required) to determine if the 'changed' product is the same, or interchangeable, with the original product. When FDA determines that the change to the reference product results in a product with the same safety and efficacy, the changed product is substituted for the original product without concern. Patients, physicians and pharmacists typically are unaware of these changes, relying on FDA to make the decision. FDA will use the same scientific approach in evaluating biogenerics. Therefore, once FDA makes an interchangeability determination, patients or health care practitioners should be confident in using biogenerics. Further, FDA should be proactive in assuring patients and practitioners that interchangeability determinations are based on sound science and that biogenerics have the same safety and efficacy. FDA can play a critical role in promoting acceptance of biogenerics.

In regard to patient access, interchangeability decisions will increase competition, affordability, and access to biologics.

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

Interchangeability determinations dramatically reduce the need for firms to engage in comprehensive marketing efforts, thereby reducing the cost of the product. Additionally, smaller firms will be encouraged to compete since interchangeability will

provide purchasers with complete confidence that the products are the same as the reference product without the need for special marketing programs, thus allowing them to compete on price and service.

To achieve maximum savings from lower-cost biogenerics, there must be robust competition in the biologics market, which results only if legislation enables a workable regulatory pathway that provides for interchangeability. Interchangeable biogenerics would give pharmacists and doctors the choice of switching from a brand to a more affordable generic equivalent, thus providing lower-cost reimbursement options to health plans, the government and other third-party payers. Refusing to enact a pathway to interchangeability would result in a system that merely encourages brand companies to produce biogeneric versions of their products. This would do little to actually stimulate competition from true generics marketed by generic companies. In short, if the U.S. adopts nothing more than an EU type "biosimilar" system, the promise of real savings from biogeneric competition will be lost.

Further, legislation that allows for interchangeable biogenerics is essential to providing the incentives technology innovators assert they need to invest and develop new and advanced characterization and process control technologies. If legislation prevents FDA from making interchangeable determinations, scientific innovation from technology companies will be held back because the incentive to innovate will not be there. Given the need for affordable, safe and effective biopharmaceuticals in the marketplace, and the need to maintain state-of-the-art science and technology to determine, at least for some products, their interchangeability, it is very important that FDA be given authority to use its expertise to make critical judgments to determine that two products are interchangeable.

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

The amount of testing will depend on the nature and complexity of the product. It would be impossible to determine a single specific list of tests that would be suitable for every potential biogeneric. The types of testing would include assessment of chemical, physical and biological characteristics, but the nature of each category would vary greatly depending on the specific product and its characteristics because technology is constantly improving and the types of tests would be expected to evolve over time.

Interchangeability connotes a degree of confidence in comparability data that allows for FDA to make distinct claims about using either the reference or biogeneric at any time, interchangeably, during therapy. The amount, type, nature, robustness, relevance and significance of a given dataset and its ability to support a claim of interchangeability is a function of multiple scientific considerations that necessarily should be left to FDA.

8. 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.

FDA must have the authority to determine interchangeability. There should not be product specific requirements for demonstration of interchangeability set forth in the statute. A case-by-case approach is necessary which allows for considerations such as the variability of the reference product, clinical use of the product and the accumulated experience, as well as structural and functional characteristics. Furthermore, technology evolves too quickly to establish product specific requirements in the law. Imposing statutory requirements could bar employing new technologies. Requirements considered appropriate for demonstration of interchangeability in 2008 will quickly be outdated and replaced with more sophisticated analytical technology.

9. 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?

When FDA approves a biogeneric it is doing so based on sound science to ensure the same safety and efficacy as the brand product. There is only one standard for safety at FDA. Again, there is not a lower standard for generic drugs or biogenerics. If FDA determines that two biologics are interchangeable, physicians, pharmacists, and patients should feel confident in their use and substitution for the brand product by pharmacists, just as they do when the brand products make a change after approval and relies on comparability testing to assure that the 'changed' product offers the same safety and efficacy as the original product.

The availability of a biogeneric would provide a lower cost alternative to a brand biologic, whose costs are often prohibitive. Greater affordability is usually associated with better drug compliance and better drug compliance means a better medical response. Greater affordability also means that a greater number of patients will have access to the important clinical benefits that biologics represent. The availability of a biogeneric would provide a lower cost alternative to a brand biologic, whose costs are often prohibitive. Greater affordability is usually associated with better drug compliance and better drug compliance means a better medical response. Greater affordability also means that a greater number of patients will have access to the important clinical benefits that biologics represent.

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 GPhA's experience, brand companies obtain numerous patents on their products. These patents provide many years of protection after product approval. For example,

FDA approved EPO back in 1989, but, according to the brand, that product still has patent protection some 20 years later.

Some may cite a July 1998 CBO study as evidence that the average effective patent term for pharmaceuticals is about 12 years. This ten year old study is not a reliable basis on which to draw a fundamental public policy/competition line that will affect consumer and tax payer medical costs annually in the tens of billions of dollars, at least. First, the study is outdated and is based only on data from 51 drugs approved between 1992 and 1995. Second, the study does not answer the relevant question. The study calculates an average effective patent term based only on how much time was left on the listed patents when each drug was approved. It does not analyze when or how soon generics could have entered the market following FDA approval of the branded drug. Thus, it does not assess the average period during which pharmaceuticals enjoy a patent-based monopoly.

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?

First, biologics have enjoyed the patent extension provisions even though there have been no provisions permitting an abbreviated approval pathway as there has been for drugs. Therefore, brand biologics have received a protected market monopoly since 1984.

In regard to a model for biologics, Hatch-Waxman has been extremely successful for the innovator industry, as well as the generic industry. It strikes a reasonable balance between market incentives and competition which provides affordable access. Hatch-Waxman provides protection beyond that afforded to any other industry and has achieved its goal of innovation and access. GPhA believes that five-year market exclusivity, along with intellectual property and the patent restoration provisions included in the Hatch-Waxman amendments, provides a reasonable balance between innovation and access and should be used for biogenerics. Hatch-Waxman has provided the U.S. with the most robust pharmaceutical industry in the world.

There are a number of lessons learned from Hatch-Waxman. Loopholes in the original law allowed for evergreening of patents and strategies to block generic competition through creative patent listings. Many of these loopholes were corrected in the 2003 Food and Drug Administration Medicare Prescription Drug, Improvement, and Modernization Act. Careful consideration must be given to the patent component of any biogeneric legislation to assure that patent issues do not prohibit FDA approval.

The Congressional Budget Office's 1998 report "How Increased Competition from Generic Drugs Has Affected Prices" detailed another key lesson learned from the implementation of Hatch-Waxman: Generic competition "has played an important role in holding down national spending on prescription drugs from what it would otherwise

have been." Considering only sales through pharmacies, the CBO estimated that by substituting generic for brand drugs, purchasers saved roughly $8 billion to $10 billion in 1994 (at retail prices). These savings have increased substantially over the past decade as generic utilization has climbed from approximately 43% in 1996 to 67% in 2007. [see http://www.cbo.gov/doc.cfm?index=655&type=0&sequence=1]

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?

Some innovators claim that patents are not enough to guarantee protection of intellectual property for biotech drugs because biologic patents primarily claim a process rather than a chemical entity, as with traditional drugs. Because it allegedly can be difficult to identify which of the process patents are relevant to a particular biogeneric application, innovators suggest that exclusivity is needed in addition to patents to ensure proper intellectual property protection for brand biologics. That is not true. Biologic products, just like traditional drug products, do not have just one or two patents, but 30, 40, or more patents. And each of these patents offer 20 years of protection to the claims they cover, regardless of the length of any exclusivity period granted. In addition, biologics are eligible for a patent term restoration of up to five years under Hatch-Waxman. As a result, valid and enforceable biotech patents offer good and sufficient intellectual property protection.

The generic industry supports the US patent system and respects legitimate intellectual property protections. Generic manufacturers, however, have endured years of patent abuse by innovators (e.g., "evergreening," double patenting, inequitable conduct, etc.) seeking to extend market monopolies. Recognizing this exploitation of patents to delay competition from generic drugs, Congress included various patent-related reform provisions in the 2003 Medicare Modernization Act. To prevent similar abuse in the biogeneric market, biogenerics legislation must include a voluntary mechanism that allows for timely resolution of patent issues initiated by the generic applicant.

Finally, GPhA is struck by the stark contrast between the brand industry arguments about patent reform legislation and biogenerics legislation. When addressing patent reform, brands argue that patents are the life blood of their industry and they need patent reform to shore up their IP protections via product patents. In contrast, when arguing the biogenerics issue, brands say patents do not mean much and, therefore, they need excessively long exclusivity periods.

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?

Patent uncertainty acts as a drag on generic product investment and market introduction. Thus, the legislation should provide a mechanism for the clear and timely resolution of patent disputes, but prohibit frivolous suits from restricting access to biogenerics and delaying competition in the marketplace. Such a system should promote informed decisions by generic manufacturers to enter the market. This goal is best achieved via a voluntary process that is initiated by the generic company. Allowing the brand company to sue on any patent prior to launch would tie the generic up for years in patent litigation. It would also significantly delay the generic's ability to obtain certainty with regard to patents that could impact generic product launch. Finally, as a matter of fairness and to make the disclosure system work, there should be a limitation on remedies with respect to any patent where the owner does not fulfill its obligations under the statutory scheme.

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?

If the generic company initiates the voluntary patent process, the brand company is in the best position to inform all relevant third-party patent holders about the fact that the process has been initiated.

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?

No. A biogeneric statute should not require FDA to administer patent listing and notification provisions as Hatch-Waxman does. Appropriate notification can be accomplished through an alternative process that does not require FDA to expend any resources.

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?

Some would argue that because biological drug development times currently can be longer than for chemical drugs, exclusivity for biologics should be longer than what is provided under Hatch-Waxman. However, the 2007 DiMasi-Grabowski study (Duke Univ. Department of Economics) shows average development and regulatory review time for chemical drugs is 90.3 months, compared with the average development and regulatory review time for biologics of 97.7 months. That is an increase in development and review time of less than eight months, or just 8%, which hardly justifies a more than doubling of the exclusivity given to brand companies from five years to 12 years, as some have proposed.

[www.innovation.org/documents/File/Grabowski_Data_Exclusivity_for_New_Biological_Entities_FINAL.pdf]

The current framework of the Hatch-Waxman Act provides a well tested rigorous model for any new legislation regarding biogenerics. The U.S. can claim to have the most robust pharmaceutical industry–both brand and generic sectors–in the world. This is due to the fact that brand patent term extension and exclusivity sections of Hatch-Waxman provide adequate incentives for the development of new drugs and improvements to these drugs.

All drugs – whether they are biologics subject to PHS Act or chemical medicines subject to FDCA – are important and should be treated fairly and equitably. There simply is no legitimate reason to give biologics companies longer exclusivity periods. For this reason, there should not be special exclusivity provisions for biopharmaceuticals in new legislation establishing a definitive regulatory pathway for biogenerics. To treat biologics differently would disrupt the carefully crafted U.S. pharmaceutical balance between providing reasonable incentives to develop new biologic medicines and the need to have biogenerics on the market in a timely manner. It would also diminish the importance of the patent system in this country for new inventions and new discoveries since market exclusivity by its nature provides an "absolute monopoly" – a definitive time period free from competitor's challenges of any form. In addition, despite claims to the contrary, the R&D time tables for biologics appear to be relatively similar to that of chemical drugs products. Therefore, there is no legitimate reason to favor the biopharmaceutical industry over all others in terms of providing to them alone a free pass to avoid reliance on the patent system as the most important vehicle to exclude competitors from using the claimed discovery.

The first Hatch-Waxman incentive provides a mechanism to restore patents covering new chemical entities. There is no question that brand pharmaceutical companies have benefited tremendously from the ability to extend a patent covering a blockbuster drug for up to an additional five years. The value of this extension is enormous. This important incentive is often ignored by BIO/PhRMA when discussing the many provisions that have benefited pharmaceutical companies while also delaying generic entry.

The next Hatch-Waxman drug development incentive is the exclusivity provisions. These provisions provide market exclusivity to the brand company for the particularly approved drug or dosage form for certain limited periods of time. These provisions were added to the Hatch-Waxman Act to encourage the development of new drug products, new uses and new dosage forms, regardless of whether or not the product, use or form was protected by a patent. In effect, they provide market exclusivity even for drugs that have no patent protection. [See 2004 FDLI 479: Drug Marketing Exclusivity under U.S. & European Union Law.]

Additionally, there is no question that the three year market exclusivity provisions have provided enormous incentives for the development of new products, new indications of

use and new dosage forms. Many of the approved drugs in the past several years that have benefited from these exclusivity provisions have been new dosage forms such as extended release versions of previously approved drugs. Most of these drugs are not "breakthrough" pharmaceuticals but, instead, are the progeny of previously approved drugs that have evolved from clever life cycle management strategies. The periods of "market exclusivity" are therefore dependent upon the type of drug, that is, for a new chemical entity the exclusivity is five years; for a new use or dosage form the exclusivity is three years. GPhA believes that the patent system in its current form enables a company to file for and obtain patent protection on its discoveries. Biopharmaceutical patents extend protection today to products via composition of matter patents (e.g., patents claiming therapeutic proteins, drug delivery matrix, isolated genes, humanized monoclonal antibodies to name a few) as well as process patents claiming methods of manufacturing and methods of using a product. In fact, PTO granted over 5170 biopharmaceutical patents in 2001, which was dramatically up from 1398 patents in 1992. Successful drug products that are patented should provide sufficient monopoly profits during the patent life (including valuable extensions thereof) in order to pay research and development costs and provide the incentive for further innovation.

Hence, there is no reasonable justification for granting unprecedented and excessive market exclusivity periods to biopharmaceuticals. Any market exclusivity terms that are longer than five years diminish the importance of and reliance upon our patent system. Providing long government granted absolute, market exclusivity terms would permit the developer of biopharmaceuticals to "double dip" by taking advantage of the absolute market exclusivity provision as well as garnering the fruits of the patent system.

Lastly, and perhaps most importantly, unlike the patent system, there is no "quid-pro-quo" provided to the public in return for a government granted market exclusivity period. The provisions would be an absolute bar on FDA from approving generic equivalents during this time period. The public is thus denied access to these generic equivalents even if there are no patents covering such products nor product data or information becomes available to the public.

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?

To date, there have been no data assessments to support the need for an exclusivity period different than what is provided in Hatch-Waxman. Even accepting the assumptions in the aforementioned 2007 DiMasi-Grabowski study – which the generic believes are questionable – there is just a minimal increase in the average development and approval time for biologics over chemical drugs (97.7 months vs. 90.3 months). We believe that any proposed increase in the exclusivity period for biologics beyond what is provided for in Hatch-Waxman must be driven by data and sound assumptions.

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

First, this assumes such changes should receive any exclusivity. Second, for the reasons cited above, to the extent exclusivity is provided, GPhA believes that the five year terms and the three year terms of Hatch- Waxman are reasonable for novel biopharmaceutical entities, new products, new uses and new dosage forms of such entities, respectively. However, careful attention must be paid to what products qualify for these considerable incentives. What benefits do innovator firms obtain from data exclusivity, and how is this protection different from patent protection?

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

GPhA supports 5-year market exclusivity, and not data exclusivity. Market exclusivity provides a period of market monopoly. FDA cannot approve a biogeneric during the exclusivity period. In addition to this considerable incentive, patent protection provides a barrier to competition provided that it is a strong and valid, enforceable patent.

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

There is no legitimate reason to favor the biopharmaceutical industry over all others in terms of providing to them a different period of market exclusivity. Providing enhanced market exclusivity provisions in any biogenerics legislation would, without any doubt, disrupt the delicate pharmaceutical balance between fostering biopharmaceutical innovation and consumer access to affordable medicine.

While BIO/PhRMA advance the misconceived notion that the U.S. should be more in line with the EU with respect to longer market exclusivity periods, several distinguishing factors make that argument unconvincing. First, the EU market is controlled by rigorous price controls unlike United States' free market. Second, the EU's patentability standards are different from the U.S., resulting in significantly less biopharmaceutical patents being granted in Europe. Third, longer market exclusivity provisions have not and, do not equate to more innovative R&D capacity. Fourth, pharmaceutical companies in the EU and in most other countries do not enjoy the tremendous benefits of the U.S. intellectually property-based generic approval system with IP linkage at its core.

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

Patents are granted for innovation and typically provide protection beyond an exclusivity period. To incentivize innovation, industry should be rewarded through the patent system. Using regulatory exclusivity as a proxy for patentability holds the risk of allowing small incremental changes to a product to receive years of monopoly protection while ignoring true innovation.

6. 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?

Again, the generic industry supports having ample incentives for new drug innovation. Generic companies are acutely aware that if new drug pipelines dry up, then future generic pipelines will be empty as well. However, unless empirical data are produced to show otherwise, current IP protections through 20-year patents and existing exclusivity periods, are adequate to incentivize new drug innovation.

Further, market competition generated by biogenerics will unleash incentives for developing new products, just as generic competition has spurred the development of new medicines in the chemical drug sector. Former Congressman Jim Greenwood, now the head of the brand biologic trade association BIO, acknowledged this recently when he said competition from generic companies "will stimulate more innovation." Former FDA Deputy Commissioner for Medical and Scientific Affairs Scott Gottlieb said legislation to expose biologics to competition would unleash innovation and "accelerate development of improved products, not just lower cost." Congressman Pallone correctly noted, "When Hatch-Waxman was enacted in '84, its detractors claimed that it would stifle innovation, yet the number of new technologies developed in the last 20 years, particularly in biologics, has been staggering."

<u>Economic Impact</u>

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.

A new economic study released in February 2008 by economist Robert Shapiro -- former Under Secretary of Commerce in the Clinton Administration and advisor to former British Prime Minister Tony Blair – estimates that potential cost savings generated by biogenerics would total as much as $378 billion over the next 20 years. The study found that generic versions of the top 12 categories of biologic drugs with patents that either have expired or are soon to expire could save Americans $67 billion to $108 billion over ten years and $236 billion to $378 billion over 20 years. The study concluded that the economic and medical benefits from generic biologics "should be as great or perhaps even greater as those from generic forms of traditional pharmaceuticals." According to a 2007 report from Citizens Against Government Waste, the total savings resulting from competition from biogenerics over the period 2011-2020 would be $43.2 billion…increasing from $1.0 billion in 2011 to $6.3 billion in 2020 as more drugs come off-patent. Other studies have produced varying levels of estimated savings, but all agree that the savings are measured in the 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?

Addressing only the cost of the generic vis-à-vis the brand reference product, an analysis performed last year by Merrill Lynch estimated that the first biogeneric would enter the market at a price 20 to 30 percent below the reference brand. As the number of generic competitors increased, the price discount off the brand would rise to 40 to 50 percent. A 2007 report by Citizens Against Government Waste put the generic discount at 10 to 25 percent in the initial year, rising to a range of 25 to 47 percent in the fifth year as other competitors enter the market. (http://www.cagw.org/site/DocServer/Biogenerics_FINAL.pdf?docID=2221). The biogeneric human growth hormone Omnitrope, for instance, was introduced at a 20 percent discount to the brand. A recent article in The New York Times noted that New York's Medicaid program spent about $500 million for insulin in 2005, and reported that had generic insulin been available, research shows the price would have been 25 percent less than the brand.

The important point is that any level of savings—even a 10% to 20% reduction in costs—would amount to tens of billions of dollars for consumers and the healthcare system over the next decade. The market for biopharmaceutical medicines is growing at an astonishing rate (more than twice the rate of traditional drugs) and now represents approximately $50 billion in U.S. sales. Annual U.S. sales of biologics are projected to hit $100 billion in three years and account for more than one-fourth of the total drug spending (April 26, 2007, Drug Trend Report). More significantly, Medicare spending for biomedicines continues to escalate disproportionately to Medicare funding. This year, for instance, Medicare Part B will spend close to $2 billion on just the biologic anemia drug Epogen, an amount approximately equal FDA's entire FY 2008 budget. Saving even 25 percent with a generic version of Epogen would lower Medicare's drug spend by $625 million.

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

The Hatch-Waxman law exemplifies a model for U.S. economic competitiveness and IP leadership at its best. Recall that Hatch-Waxman is titled the "Drug Price Competition and Patent Term Restoration Act." The patent term restoration (patent term extension) portion of the law gives patent holders the opportunity to extend the length of patents and IP protection, thus giving brand companies added incentives to innovate. Every year, several brand drug patents are extended (by up to five years) by the PTO. The other part of Hatch-Waxman created the modern generic industry, which provides thousands of lower-cost medicines to consumers. This carefully crafted balance has worked very well for more than two decades in the chemical drug sector, resulting in new drug development as well as billions in savings. This same balance would work equally well in the biologic sector.

4. What implications does the treatment of patents in the context of a follow-on biologics approval pathway have for the future of biotechnological innovation?

   Legislation creating a pathway for biogeneric products would not impact the protection afforded by the patent laws to valid, enforceable patents covering brand products.

5. If a follow-on biologics pathway was created without ample incentives for innovators to continue to innovate, what would the effect be for future research, current clinical programs, and universities?

   The generic industry is not advocating an approval pathway without ample incentives for innovation. There would be no generic product without a brand product, so it is in the best interest of generic companies that brand companies continue their innovation of new drugs. Likewise, it is in the best interest of patients, taxpayers, healthcare providers and the government that lower-cost generic versions of medicines are allowed to come to market after legitimate patents and reasonable IP protections on brand biopharmaceuticals expire. And, as discussed above, Hatch-Waxman should be used as the model for any additional incentives provided to brand companies for biologic products.

<u>European Model (abbreviated approval pathway)</u>

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.?

   First, guidance development is a slow and painstaking process requiring substantial FDA resources. Human Growth Hormone and Insulin guidances have been in development at FDA since the late 1990s and have yet to be issued. It would realistically take several years before FDA could issue product specific guidances. Requiring issuance of guidances before FDA acceptance of biogeneric applications will unduly delay firms wishing to submit applications for biogenerics for years.

   Interestingly, there is no other mandate that guidances must be published before submitting applications for new drugs or biologics. Rather, applicants can use good scientific principles in product development regardless of the complexity of the product. While guidances can be helpful, firms should be able to submit applications for biogenerics whether or not a guidance exists.

   For the most part, guidances typically have little relevance to healthcare providers and patients since these documents address very specific analytical or clinical issues. Patients and physicians more often rely on product labeling to assess a product.

GPhA does not have any information on whether the EU guidance process provides any benefit to healthcare providers or patients and is not aware of any assessment on this topic.

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

The EU and U.S. drug approval systems are entirely different. Price controls are a major component of the EU system. Price controls typically limit an innovator's return on investment which arguably could justify longer market certainty. Since the U.S. does not have price controls, innovator company profits are not capped as they are in the EU which permits a higher rate of return. Maintaining an extended market monopoly in a free market environment is not justifiable. Again, the U.S. patent law provides more protection than the EU system

3. If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, what could the potential effect be on U.S. competitiveness?

As noted above, each region in the EU has different systems for pricing and for payers. Currently, the EU provides longer market exclusivity for drugs than does the U.S. Nevertheless, the U.S. pharmaceutical industry has maintained a high level of competiveness and profitability. Additionally, GPhA is unaware of any data confirming that development of a biologic product takes substantially longer than for a small molecule product. In the absence of such data, there is no basis for extending the monopoly period for an approved biologic in 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?

The EU system differs in a number of important ways compared to an optimal system for the U.S. In regard to patient safety, FDA should have the flexibility to require the data that is necessary to assure safety and effectiveness of biogenerics. This flexibility will allow FDA to establish the data requirements on a case-by-case basis. With the free market environment in the U.S., longer exclusivity periods would tip the balance of innovation and access clearly in favor of the brand firms and delay patient access to more affordable medicines. Therefore, periods of exclusivity comparable to the EU are unwarranted. The EU also requires mandatory guidances before biogeneric applications can be accepted for review and is not necessary under the U.S. approval system, which is different than the EU system.

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?

GPhA is not aware of any reports from Europe regarding safety or efficacy issues for products approved as 'biosimilars.' In reviewing the literature and EMEA reports, GPhA was unable to identify any negative reports related to safety or efficacy of biogenerics. Likewise, GPhA is not aware of any problems with the protein products approved under FFDCA based on an abbreviated data package. In addition, in the EU, the approval for biosimilars system is centralized whereas market access and pricing differ per country. There is not one EU-wide pricing system, but rather a number of different price control mechanisms in the various countries.