Johnson & Johnson's Responses to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health

This submission is made by the Johnson & Johnson family of companies in response to questions posed by the House Committee on Energy and Commerce on biosimilar products. We appreciate the opportunity to submit these comments. Johnson & Johnson companies include world leaders in the research and development of biotechnology-derived medicines and have extensive experience with the scientific and technical issues relating to those products.

We answer below each of the Committee's questions, sometimes grouping them to avoid duplication or overlap. We wish, however, to emphasize three key points. First, protection of patient safety must be at the heart of any system for the approval of biosimilars. Biosimilar products present fundamentally different scientific and technical issues from generic drugs. Their active ingredients and formulations will ordinarily differ from those of reference products in ways that can affect safety and effectiveness. The only means of assuring that biosimilars do not present a risk to patients is to require preclinical and clinical testing, as has been done in the European Union.

Second, to ensure that standards for testing of biosimilar products incorporate the best available scientific information, requirements must be developed through open and transparent procedures that permit participation by all interested persons, including manufacturers of reference products, medical specialists, and academic experts. The most efficient means of accomplishing this is through public proceedings on guidelines for each category of biosimilars, as has been done successfully in Europe.

Finally, a system for approval of biosimilars must preserve incentives for research and development of new biotechnology medicines. The U.S. biotechnology industry is the most productive in the world, and it has yielded medicines of immense importance to public health. Any legislative system must avoid undermining rights currently protected by patent law. It is equally important to recognize the key role of data protection -- that is, a period after approval of innovative products during which biosimilars cannot be approved based on reliance of safety and effectiveness data developed by innovators. This is especially important in the biotechnology sector, because patents are often narrowly drawn and biosimilar products will often differ in their structural features from reference products, thus increasing the likelihood that they will circumvent patents.

I. Science/Safety

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

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

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?

These paragraphs respond to questions 1 through 3. Immunogenicity is the potential for all biological products to stimulate an immune response in the body, prompting the formation of antibodies. This is a desirable feature for vaccines where the intent is to stimulate an immune response leading to the patient developing protective antibodies against bacteria and viruses such as tetanus and rubella. In most therapeutic proteins immunogenicity is not desirable, and the development of immune reactions can result in serious, and potentially fatal consequences such as acute anaphylactic reactions and serum sickness type reactions including joint swelling, fever, and encephalitis. Less common but equally important is the occurrence of antibodies following exposure to a therapeutic protein that can neutralize (inactivate) the therapeutic protein or cause it to be cleared more quickly from the body, resulting in a loss of efficacy and progression of the disease. For example, patients with hairy cell leukemia treated with interferon alfa have been reported to experience a relapse of the disease when neutralizing antibodies form. In addition, and more serious still, for certain biological products, neutralizing antibodies can inactivate the body's naturally occurring protein, resulting in adverse and even life-threatening side effects. For example, volunteers who received an experimental biological version of thrombopoietin, a protein that stimulates production of platelets critical for blood clotting, developed antibodies that neutralized not only the product but also their own naturally produced thrombopoietin, which resulted in bleeding problems.

Immunogenicity is particularly important in the context of manufacturing changes for a biological product, because product differences that are difficult or impossible to detect analytically in the laboratory can lead to differences in immunogenicity in patients. As explained above, this in turn can affect the safety and effectiveness of the product. The development of antibodies, and their effect on safety and effectiveness, can be assessed only through clinical testing, and even then sometimes cannot be fully assessed through a reasonable program of premarket testing. The case of EPREX®, a biological product sold outside the United Sates by Johnson & Johnson companies, illustrates how even a seemingly minor change can increase a product's immunogenicity and cause harm to patients. In 1998, our company changed the stabilizer in its EPREX formulation at the request of European authorities because of concern in Europe that the existing stabilizer, human serum albumin, could theoretically transmit Creutzfeld-Jacob disease (a human form of Mad Cow disease). The switch from the old

stabilizer to another well-established stabilizer seemed to be a minor change, and it was intended to improve the product's safety profile. Shortly after this seemingly minor change, however, there was an increase in the incidence of antibody-mediated pure red cell aplasia (PRCA) among patients taking EPREX. PRCA is a serious condition in which bone marrow ceases to produce red blood cells and patients were reliant on blood transfusions for survival. It took four years of extensive investigations to identify the likely cause. Uncoated rubber stoppers, when exposed to the new stabilizer, released substances called leachates into the EPREX formulation, and those substances likely increased the product's immunogenicity, resulting in an increase in PRCA.

In sum, many types of manufacturing changes can affect the immunogenicity of a product, the consequences of which can be clinically important, while other changes (for example, substitution of identically designed equipment in a production line) have a negligible risk of immunogenicity. For this reason, regulatory discretion is appropriate with regard to requirement for immunogenicity testing for manufacturing changes. FDA appropriately exercises its discretion with respect to changes made by manufacturers to their own products, often requiring clinical testing before a changed product may be commercially distributed and always requiring clinical data to support a major change (like use of a new manufacturing facility or new master cell line) – immunogenicity assessments are invariably a key part of this exercise. The authority to require these data flows in part from section 506 of the FDCA, which governs manufacturing changes made by an NDA or BLA application holder to its own product.

While, as noted, some manufacturing changes made by a manufacturer to its own product are so minor as to raise negligible risk of immunogenicity differences, changing manufacturers (as is the case when a biosimilar is proposed) invariably involves changes that, in the aggregate, carry substantial risk of change in immunogenicity — for example, a new site, new materials, or new master cell bank. In these situations it is inconceivable that FDA would allow the distribution of biological products after a change in the manufacturer without immunogenicity testing.

Because the production of biosimilars requires a completely new manufacturing process to be established, and due to the known importance of the process in defining the final product, biosimilars will not — indeed cannot — be identical to the products on which they are based. There will be differences between the products, both detectable and undetectable. Because our immune systems are exquisitely sensitive to differences in protein products, including differences that are not detectable analytically in laboratory testing, it is inconceivable that safety and effectiveness could be assured in these products without testing in patients and, in particular, immunogenicity assessments. At the same time, stakeholders should understand that some extremely rare immunologically mediated adverse effects may not be detectable in any reasonable course of premarket testing. Thus, while an immunogenicity assessment should be

required in any premarket approval package, postmarket surveillance will always be necessary, and postmarket clinical studies may also be warranted.

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?

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?

This paragraph responds to questions 4 and 7. Biosimilars legislation in the United States should require clinical data from testing in each indication and patient population, regardless of mechanism of action. An applicant should be required to show that its biosimilar has the same mechanism of action as the reference product on which it is based, if the mechanism is known. It is important to acknowledge that although the mechanism of action leading to efficacy may be the same in various indications, the mechanisms for adverse reactions may be very different. Therefore, it is not scientifically correct to presume that if a drug has the same mechanism of action in two conditions, evidence of safety and effectiveness in one condition can be used to establish comparable safety and effectiveness in the other. There are very important factors such as patient co-morbidities, concomitant therapies and population specific risk factors that can lead to differences in both safety and effectiveness.

With respect to extrapolation of safety, for example, the case of EPREX is illustrative. EPREX is used to correct anemia in patients with cancer and in patients with renal failure. In both patient populations, EPREX and other erythropoietins work to correct anemia through the same mechanism of action: by stimulating more blood cell production in the blood marrow. Pure Red Cell Aplasia — in which bone marrow ceases to produce red blood cells — is, however, seen predominantly in patients with renal failure and not in patients with cancer. This is likely due to the fact that patients with cancer are undergoing chemotherapy which suppresses the immune system and decreases immune responses to the product. Also the duration of therapy in cancer patients is much shorter than for patients with renal failure. If a biosimilar version of EPREX were studied only in patients with cancer and found to be "comparable" with an approved erythropoietin, allowing its use in patients with kidney failure might result in immunogenicity and serious safety problems in those patients. A similar situation is observed in granulocyte-monocyte colony stimulating factor, or GM-CSF, a biological product that stimulates some bone marrow and blood cells. Like EPREX, GM-CSF is immunogenic when used in some diseases and not in others. European regulators, who recently finalized a guideline on immunogenicity assessment of biotechnology-derived therapeutic protein products, following public comment and input from medicines

agencies throughout the European Union, have thus concluded that "immunogenicity evaluation needs to be studied individually for each indication/patient population."

Extrapolation of efficacy data from one indication to another is equally problematic, even when the relevant mechanism of action is known and considered identical. Even where similar biological products have the same mechanism of action (for example, they are both anti-inflammatory, anti-proliferative, or anti-angiogenic), minor structural differences between the products — such as those affecting charge and hydrophobicity — may affect how each distributes through the body. For example, products that kill tumor cells with the same mechanism of action but cross into the brain differently could have similar effects in tumors that do not metastasize to the brain but very different effects in tumors that do predominantly metastasize to the brain.

In sum, it is neither scientifically sound nor safe for patients for FDA to approve a biosimilar for all indications with the same mechanism of action after a demonstration of similarity to the reference product in just one indication.

5. Under the Food and Drug Administration Amendments Act of 2007, Congress established new authorities for FDA to enforce drug safety. How should the new post-market authorities enacted in this legislation be applied to FOBs? Are post-market studies always needed for FOBs? Are there situations in which FOB applicants will need to conduct post-market studies that are different from those that have been required and/or requested for the reference product?

The FDA will need to have latitude for discretion in applying postmarket study requirements for biosimilars. This is because the consequences and risk of adverse reactions such as immunogenicity related reactions vary depending on the method of use and the product class. For example, in the case of a single use only biologic injection, the risks of neutralizing antibodies would be extremely low and clearly not warrant extensive postmarket surveillance. In the case of chronically administered products this risk would be significantly higher and warrant closer attention. It is critical to recognize that due to the inherent complexity of biologic products, and the dependence of the product on specific processes, that FDA will need to accept a different standard for biosimilars than for small molecule generics. The standard applied to small molecule generics is that one should not require a generic company to conduct postmarket studies not required of the innovator. The standard for biosimilars should be to require sufficient data to reasonably exclude immunogenicity related reactions occurring at a greater frequency than the innovator, regardless of whether the innovator has an identified safety concern. Similar standards should apply to the innovator with respect to major process changes.

Because a biosimilar will not be the same as the reference product on which it is based, the postmarket risk management steps for the biosimilars may be different from those required for the reference product. For example, postmarket experience with the reference product may give rise to concerns about a particular type of

immunogenic response that should be addressed through a postmarket risk management plan (such as patient monitoring) for biosimilar versions. In addition, innovative products typically reach the market after testing in a large number of patients. Because a smaller premarket clinical program will be permitted for a biosimilar, postmarket surveillance and antibody testing are essential to reach a comparable level of assurance about patient safety. Finally, safety concerns unique to the biosimilar may not be fully anticipated at the time of its approval and may require the development of data beyond those originally requested for approval. It is therefore essential that FDA have authority to require data relating to new safety concerns from biosimilar manufacturers, both at the time of approval and as issues emerge in the postmarket period.

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?

Given the current state of science, biological products that are produced by different manufacturers — including biosimilars and the reference products on which they are based — should bear distinct names. Distinct names are needed for two reasons. First, in the present state of scientific knowledge, biological products from different manufacturers can not be interchangeable, due to differences in starting materials, manufacturing processes, and other factors that can result in different clinical effects, including differences in potency which may be important to patient care. Distinct names will help ensure that interchange does not occur without the knowledge of the patient and their physician, simply because prescribers and dispensers assume that products with the same name are identical. Second, new biological products, including biosimilars, are typically approved with insufficient premarket testing to detect rare, but potentially serious, differences in side effects, including immunologically mediated effects. It is critically important to be able to associate specific products with adverse reactions in order to accurately define and manage risk. The assurance of safety of biological products thus depends, even more than the assurance of safety of ordinary drugs, on pharmacovigilance and other postmarket surveillance measures which rely heavily on accurate product identification.

Because of potential differences between similar products, it is essential that, when a safety signal is identified in the postmarket period, public health authorities and manufacturers have the ability to determine to which product, and manufacturing process, it is connected. Barring that, a safety concern arising in a single product could lead either to inadequate public health response or to a response that diminishes use of important medicines that do not present the same safety concern.

There are several ways to ensure that biological products bear distinct names. First, the United States Adopted Name (USAN) and World Health Organization

International Nonproprietary Name (INN) processes could be modified to ensure that each biological product bears a distinctive non-proprietary name. Under current law, this name would appear in the packaging and labeling. Second, policymakers could take steps to encourage the use of brand names in packaging and labeling, at least where the USAN and WHO processes do not result in distinct nonproprietary names. Third, where the INN or USAN systems are unable to indicate product differences in a way consistent with their taxonomy, FDA could adopt a distinctive "official name" for each product to replace or supplement the nonproprietary name adopted through USAN and the WHO. Finally, policymakers could require FDA to ensure that the labeling and packaging contain a unique name, and this could ultimately be accomplished through use of a special alphanumeric suffix to the official nonproprietary name.

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?

Biotechnology-derived therapeutic protein products have an inherent degree of structural heterogeneity due, in part, to post-translational modifications. Typically, an innovator characterizes its finished product by demonstrating a consistent range and pattern of product heterogeneity. The approved BLA therefore includes detailed specifications that establish limitations on batch-to-batch variability in light of that characterized range and pattern of heterogeneity. This ensures, in part, that batches manufactured for commercial use are comparable to those used in clinical trials supporting the BLA, especially pivotal clinical trials. The analysis of batches of a biosimilar product cannot be considered in the context of the batch-to-batch variation and the specifications of the innovator product and it is not sound science to do so. Production of the biosimilar will begin with different starting materials and involve different manufacturing processes, and the resulting product will exhibit its own range and pattern of heterogeneity. The biosimilar manufacturer will need to characterize its finished product by demonstrating its consistent pattern of heterogeneity, determine its limitations on batch-to-batch variability, and establish its specifications in conjunction with its supporting clinical data.

It is impossible to generalize about "variability in chemical structure" due to postmarket manufacturing changes. These changes can range from very minor variations in the manufacturing process to substantial changes, including changes in master cell lines or other starting materials and use of entirely new manufacturing facilities. Requirements for testing to demonstrate comparability depend on the extent and nature of the changes made. When major changes are made, it is almost always necessary to perform clinical trials to demonstrate comparability.

The manufacture of a biosimilar product cannot be analogized to the manufacture of an innovator product following a manufacturing change. The biosimilar

manufacturer has access only to the marketed version of the finished reference product, usually containing inactive ingredients as well as the active substance. It may not even be able to determine the characteristics of the active substance used in the reference product (as opposed to the active substance contained in the finished drug product, which may differ due to interactions with inactive ingredients and other factors). A biosimilar is an entirely new product, manufactured using different starting materials, a different manufacturing facility, different manufacturing processes, and different specifications for the active substance and finished product formulation from those used for the reference product. Thus clinical data to support the biosimilar will be necessary to assure that patients receive products that are shown to be safe and effective.

9. Should human clinical trials be mandated by statute for all FOBs or should FDA be given discretion [to determine] 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?

Some level of comparative clinical testing of every biosimilar with its reference product should be required. The manufacturer of a biosimilar will face several limitations in its ability to identify clinically important differences without conducting clinical trials. When a manufacturer makes substantial changes in its manufacturing process, that manufacturer is able to compare not only the final products but also various components and intermediates that are produced during various stages of the new and old manufacturing processes. Depending on the changes made, for example, comparisons might be made of the unpurified biologics and/or the purified products prior to formulation. These comparisons may detect important differences that remain in the final product but at levels that cannot be detected through analytical comparisons. Manufacturers of biosimilars will not have these materials for testing and will have access only to the final marketed reference product. In addition, optimal comparisons of before-change and after-change materials require an understanding of the parameters that are key to the safety and effectiveness of the molecule and the best ways to measure those. This understanding comes from years of working with the reference molecule and is not available to the biosimilar applicant. Finally, manufacturers of innovator products typically have extensive experience with their products, which helps them determine whether identified differences are clinically important. Biosimilar applicants also lack this experience.

For these reasons, there will be a need for the foreseeable future for some amount of clinical testing of biosimilars. The amount and nature of testing will depend on the product. It is inconceivable at the present time that any biosimilar would be found to meet the current licensure standards of safety and effectiveness without some degree of testing in human subjects.

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?

A small number of therapeutic proteins, including both naturally derived and biotechnology-derived therapeutic proteins, have been approved under the FDCA. These include both naturally derived and biotechnology-derived insulin products and somatropin products, as well as conjugated estrogens, menotropins, and urofollitropin. The FDCA requires substantial evidence of effectiveness to support any new drug application under section 505(b), and this is defined to mean adequate and well-controlled investigations, including clinical investigations. To our knowledge, all innovator therapeutic protein products — whether naturally derived or recombinant — have therefore been supported by clinical data.

We are aware of only one application for a naturally derived therapeutic protein product submitted and approved under section 505 without any clinical data. This was a unique situation, and the product was never marketed. FDA has not approved a therapeutic recombinant protein product without clinical data.

In 1997, FDA approved an abbreviated new drug application (ANDA) for Repronex, a generic version of the drug Pergonal (menotropins) intended for intramuscular administration. At that time, menotropins had over 30 years of U.S. marketing experience. FDA relied in part on publicly available clinical data to reach the conclusion that Repronex was the "same as" its reference product, Pergonal (menotropins), for purposes of section 505(j). Shortly after ANDA approval, however, Repronex's manufacturer received approval of an NDA for subcutaneous administration of Repronex under section 505(b)(2). The NDA was supported by data from two original clinical trials. The ANDA product was never marketed and, since then, biosimilar applications have been submitted under section 505(b)(2) and supported by clinical data. Further, FDA has consistently refused to approve an ANDA for a generic version of Premarin, a naturally derived conjugated estrogen product.

Although FDA has approved two biosimilar applications submitted under section 505(b)(2), both products were supported by extensive clinical data. Omnitrope and Fortical were comparatively small and simple proteins, well understood, relatively characterizable, and not glycosylated. Although the applications were 505(b) applications subject to the requirement to demonstrate both safety and substantial evidence of effectiveness, FDA permitted each applicant to rely in part on preclinical and clinical data submitted by an innovator in support of a reference product. Each applicant, however, also submitted clinical data of its own. The Fortical application relied on clinical data obtained from three Phase III clinical trials as well as two immunogenicity studies. The Omnitrope application contained data from six original Phase III trials (three in healthy adults and three in children with growth hormone deficiency).

11. Omnitrope is approved in the U.S. (albeit as a 505(b)(2)) and in Europe (as the first biosimilar). Have patients experienced any problems? Have patients been switched to Omnitrope from other recombinant human growth hormone products? If the answer to part b is yes, how are payers handling the availability of this comparable product?

We do not have information about patient experiences with Omnitrope. It is worth noting, however, that during clinical testing the manufacturer of Omnitrope determined that active substance manufactured at one facility contained a higher amount of host cell proteins than active substance manufactured at another facility and was significantly more immunogenic in patients. Changes to the manufacturer and manufacturing process were apparently necessary to decrease the host cell protein content, which appears to have reduced immunogenicity. There are published reports of similar findings several decades ago, when innovators were first developing biotechnology-derived human growth hormone products, which illustrates the fact that decades of published experience with a molecule cannot substitute for immunogenicity assessments in humans of the particular product at issue

II. 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?

Biosimilars legislation should provide an exclusive pathway for follow-on versions of any biotechnology-derived therapeutic protein that is approved under either of the statutes administered by FDA — the PHSA or the FDCA. Approval of NDAs for a handful of therapeutic proteins, like insulin and human growth hormone, was the result of a series of ad hoc decisions made by FDA. It did not reflect a conscious agency decision to subject those proteins to a standard that is different from the standard that applies to other therapeutic proteins. Biosimilars raise a variety of issues not raised by small molecule drugs. These include — for example — special issues relating to the inability to completely characterize, the need to verify clinical similarity despite incomplete analytical similarity, and the need for immunogenicity assessments with respect to every indication and patient population. Biosimilar applications will also vary in size and complexity, and FDA — with statutory guidance and public input — should specify the contents of applications on a product–class by product–class basis. These public health considerations are generally true of recombinant proteins approved under the FDCA, just as they are of recombinant proteins licensed under the PHSA. Applying the new biosimilar scheme equally to FDCA and PHSA proteins will ensure the same regulatory standards and public scientific processes apply to similarly situated products.

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

FDA routinely requires clinical trials to demonstrate comparability when major changes to approved products are made in starting materials, manufacturing processes, or manufacturing facilities. As not all changes are extreme, discretion is appropriate and, to our knowledge, has been adequate to protect safety. A biosimilar will, however, always present an extreme example of such changes: the biosimilar will be produced from different starting materials, in an entirely different manufacturing facility, using a different manufacturing process, and with different specifications for the active substance and finished product from those used for the reference product. Consistent with long-standing FDA practice, it is inconceivable that a product representing such an array of fundamental changes could be approved without clinical trials.

3. What FDA office should review FOBs?

6. How much in additional appropriations or user fees would FDA need to implement a generic biologics program? What proportion of resources should come from user fees? How would that relate to the user fees that are assessed for traditional drugs and/or biologics?

This paragraph responds to questions 3 and 6. Because biosimilar applications will contain quality data, preclinical data, and clinical data, they should be reviewed by the review divisions that have responsibility for the reference products on which they are based. Like the review team that examines an innovative BLA, the review team responsible for a biosimilar application will likely consist of chemists, pharmacologists, toxicologists, clinicians, statisticians, clinical pharmacologists, and biopharmaceutists. Efficient review of these applications can occur only if FDA leverages its existing expertise, although protections will need to be in place to ensure that trade secret aspects of the reference product application are not used to support approval of the biosimilar application. In any event, timely review and approval of biosimilar applications will require both substantial expertise and considerable additional resources, which will in turn require both appropriated funds and user fees comparable to those paid by innovators.

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?

Because even seemingly modest changes to a complex protein or the manufacture of the product containing that protein can result in immunogenicity with potentially devastating public health consequences, biosimilar applicants should not be permitted to deliberately modify the proteins or the products unless they are prepared to submit full BLAs with supporting clinical data packages. Instead, the goal for the biosimilar applicant should be to achieve the closest degree of similarity scientifically possible and to fully assess the clinical impact of any differences that are technologically unavoidable. FDA can and does work with the scientific community, other public health authorities, reference product sponsors, and biosimilar manufacturers to determine the full range of analytical and biological tests that can be applied to fully characterize the active ingredients and products for this comparison

It is not possible to make two biological products identical, so biosimilars legislation will inherently allow abbreviated applications for molecules that are no more than highly similar to a reference product. There is no scientific basis, however, for allowing abbreviated testing of a new product on the grounds that it is distantly related to an existing one. As a scientific matter, some differences are so substantial that the biosimilar product should be considered a new product that requires a full BLA. A variation in amino acid sequence, for example, creates a new drug, because the amino acid sequence defines the protein. Indeed, differences in just one amino acid can have major effects on the function of a protein. The AspB10 insulin analogue is a prime example. This complex protein varied from human insulin with respect to only one amino acid, yet surprisingly it triggered the development of breast cancers in laboratory rats. To give another example, post-translational events — such as glycosylation — can have a major impact on the activity, half-life, and immunogenicity of a complex protein. For many products, a difference in post-translational modification will require significant clinical testing to determine its clinical impact, and many differences are so profound that they should be considered to make the biologic a different product, requiring a full BLA.

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?

It is critical for public confidence and to ensure patient safety that regulations and guidance be in place prior to FDA approving applications to ensure a consistent and transparent standard is applied and we do not end up with two tiers of products with respect to public confidence and risk.

We believe that requirements for testing and approval of biosimilars should be established through an open and transparent process, similar to that which has been used in the European Union. All interested parties, including manufacturers of reference products, biosimilar manufacturers, physicians, patients, and the academic community, should be permitted to comment on draft guidance issued by FDA describing general principles for all biosimilars as well as draft guidance for each product class providing the framework for applications in that class. In particular, manufacturers of reference products will often have information derived from years of experience with process changes and comparability exercises, nearly all of which will be unavailable to biosimilar manufacturers and much of which may not be known to FDA (because changes that failed comparability testing were never proposed to the agency).

The best way to accomplish this is by requiring FDA to conduct a public guidance-development process for each class of biological product before approving applications for biosimilars. The process need not be unduly time consuming as many of the issues to be discussed have already been addressed in the EU, which completed most biosimilar guidelines in 12 to 18 months without the advantage of leveraging prior scientific and regulatory experience. If the legislation establishes a reasonable period of data protection before biosimilar applications are accepted, there should be ample time for FDA to develop product-specific guidance.

III. Interchangeability

1. Does current science permit an assessment of interchangeability (substitutability) for any biologics at this time? What is the likelihood that interchangeability assessments for some or all biologics will be possible in the future, and in what period?

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

3. How should product-specific requirements for demonstrating interchangeability be established? Should the statute prohibit interchangeability assessments or give FDA the authority to determine interchangeability as science permits? Please explain your answer.

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

5. What are the potential risks to patients from interchangeability of one biologic for another? If FDA finds two biologics interchangeable, should physicians, pharmacists, and patients feel comfortable with substitution by

pharmacists? Why or why not? How would interchangeability affect patient access to biologics?

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

These paragraphs respond to all of the committee's questions regarding interchangeability.

The Hatch-Waxman amendments did not address therapeutic equivalence or the interchangeability of generic small molecule drugs. By 1984, the agency had already issued the Orange Book, which lists approved drug products and provides therapeutic equivalence ratings. FDA uses these ratings to convey its conclusion that one product can be substituted for the other with the full expectation that it will produce the same clinical effect and safety profile. Under scientific rules established by FDA in the 1970s and early 1980s, this generally requires that the two products have identical amounts of the same active ingredient in the same dosage form and same route of administration; that they meet compendial or other established standards of strength, purity, quality, and identity; and that they are bioequivalent. In short, by 1984 FDA, working publicly with stakeholders, had already largely determined how to evaluate therapeutic equivalence in the small molecule setting. There was no need to address the issue in the generic drug approval legislation.

By way of contrast, to date neither FDA nor public health authorities in Europe have determined how one could show that two biological products are interchangeable. Indeed, the EMEA has advised that biosimilars are not to be regarded as generics, and every European national government that has considered the issue has decided that biosimilars are not interchangeable with or substitutable for reference products (or for other biosimilars). In our view, no amount of non-clinical testing of a biological product can ensure or predict that it will have effects identical to those of another product. In fact, although clinical testing can place limitations on the possible extent of differences, for most products only extremely extensive comparison studies — i.e., very large head-to-head clinical trials — would rule out clinically significant differences. At this time, in short, there is no realistic potential for a scientifically valid determination of interchangeability of biological products. Accordingly, it is our position that biosimilars legislation should preclude interchangeability determinations unless and until the agency has reached a conclusion — working publicly with stakeholders — about both the data to be submitted and the nature of the conclusions to be drawn.

A statutory and non-science-driven standard for interchangeability would encourage substitution of biosimilars for reference products, which would be dangerous for patient safety and public health. As FDA explained in September 2006, different large protein products with similar molecular composition can behave differently in

people, and substitution of one for the other can result in serious health outcomes, including generation of a pathologic immune response. Immunogenicity is a complex attribute depending on many properties, not well understood, of both the product and the recipient. Even if two products appear to have highly similar immunogenicity rates (for example, 5 percent), it is quite possible that they are immunogenic for different reasons and in different patients, so that patients exposed to both products (through substitution) would be exposed to a risk as high as 10 percent. Other risks resulting from substitution include underdosing or overdosing due to differences in biodistribution.

Indeed, even without interchangeability determinations, following enactment of this legislation, depending on state laws, substitution may occur without the consent of the prescribing physician. Unexpected outcomes due to differences between the products could lead the physician to make dangerous adjustments in therapy. For example, if a substituted product led to underdosing, the prescriber might adjust the dosage higher, which might lead to a dangerous overdose in the event of a subsequent substitution back. For this reason, in addition to precluding interchangeability determinations, the legislation should ensure that labeling and packaging clearly differentiates between biological products. This will allow prescribing physicians to select the appropriate product for their patients and be assured that substitution does not frustrate their treatment objectives.

A statutory and non-science-driven standard for interchangeability would also severely impair the ability of the pharmacovigilance system to deal with emerging safety issues. When a new adverse event emerges or a known one increases in frequency, it may be impossible to attribute the adverse event to a specific product, if patients experiencing the event have received multiple products. This is especially true for some types of adverse events, like those due to immunogenicity, that tend to arise in patients well after initial administration of the causative product. The inability to link the adverse event to the causative product could have devastating public health consequences. For this reason as well, the legislation should preclude interchangeability determinations.

IV. 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?

We do not have information on overall effective patent term for approved pharmaceuticals. Our experience is that the effective patent life varies considerably from product to product.

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?

We have taken questions 2 and 3 out of order.

For several reasons, although extremely important, patents will play a different role in the biosimilars context than they do in the generic small molecule drug context.

First, as the question suggests, the active ingredient of a biosimilar will not necessarily be identical to the active ingredient of its reference product. In the Hatch-Waxman setting, the generic small molecule product must be the same as the reference product in order to be approved under an ANDA. This sameness requirement — although driven largely by scientific concerns — has had the effect of supporting effective patent protection for innovator drugs. This is because to be the "same," the active ingredient of the generic small molecule product invariably falls within the scope of the patent that the innovator holds for the compound. In the biological product context, however, this regulatory complement to the patent is problematic. Provided an appropriate degree of similarity is established, the legislation will permit the biosimilar manufacturer to rely on the data from clinical testing of the reference product even though the biosimilar product is not the "same" in all respects as the reference product. In other words, biosimilars legislation may allow for the circumvention of patents directed to the active molecule, while the Hatch-Waxman amendments normally will not.

Second, in this context, the relevant active ingredients are large macromolecules, and patents for these products are often narrowly tailored, or are protected only by process patents that may or may not be subject to circumvention. Early innovators in biotechnology sometimes received broad patents to cover their products. The number and types of biotechnology patents issued through the 1990s grew explosively, and the scope of the claims has generally become more narrowly drawn as a result of stringent disclosure and enablement requirements and the accumulation of prior art in the field. One example relates to Synagis (palivizumab), a monoclonal antibody indicated for the prevention of serious lower respiratory tract disease in children. The patent claim for this product requires an infringing antibody to bind to the same specific binding site, or epitope, as the Synagis antibody. Another example relates to Rituxan (tituximab), a monoclonal antibody approved for the treatment of non-Hodgkins lymphoma. The claim covering this product relates to the use of a particular deposited cell line. Recent developments in patent law more generally are also driving the system towards issuance of more specific patent claims for all products. In the context of biosimilars, where scientific and regulatory provisions may permit reliance on innovator-owned data despite differences in product or process, this specificity in patent claims may mean innovators will be protected from biosimilar competition only by data protection.

For these reasons, although biotechnology patents will continue to play an important role in rewarding invention, data protection may be essential to ensure innovators can recoup their subsequent investment in research and development.

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?

Although the 14-year term of patent term restoration is helpful, as explained above in our response to question 3, although extremely important, patents will play a different role in the biosimilars context than they do in the generic small molecule drug context. As stated above, because the scientific and regulatory provisions of this legislation will permit reliance on innovator-owned data despite differences in product and process, biosimilar applicants may be able to avoid patents covering the reference product or the process used to make it and obtain approval to market long before those patents have expired. If policymakers wish to encourage the investment of time and resources required to bring patentable biological inventions to market in the form of new human medicines, a robust period of data protection — to complement the uncertain patent protection — will be necessary. As explained in our response to question 2 in the next section, a data protection period of 14 years may be helpful to provide the necessary incentives. In our experience, also, the Hatch-Waxman provisions (particularly the generic exclusivity provisions) have created enormous incentives to challenge innovator patents very early in the market life of new molecular entities. These early patent challenges divert company resources from research and development. As explained in our response to the next three questions, the present legislative discussion provides an opportunity for policymakers to draft patent resolution provisions that do not result in protracted private debates over which patents are actually relevant in the first instance.

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?

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?

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?

These paragraphs respond to questions 4 through 6, which relate generally to the structure of the patent provisions of biosimilars legislation. Generally speaking, there are three issues to resolve in the patent provisions of the legislation: how relevant patents are to be identified and by whom; when litigation to address those patents should begin; and what consequences should flow from a finding that a patent is both valid and infringed. Although there are several possible ways to write the patent provisions, any approach should be informed by the following principles: (1) there must be a robust period of non-patent data protection to protect the resources invested to bring the patented invention to market in the form of a safe and effective human medicine; (2) BLA holders and third party patent owners must learn of submitted applications during the data protection period and must have a meaningful opportunity during the data protection period to review the applications and evaluate the proposed products in order to identify patents that may be infringed; (3) patent litigation should be made possible during the data protection period through creation of a statutory act of infringement tied to the applicant's claim that such a patent is not, in fact, infringed, or is not valid; (4) this should occur early enough to ensure that the patent litigation can be concluded before the data protection term expires but not so early as to deprive the BLA holder and patent owner of a meaningful period of quiet enjoyment of the patent; (5) if a patent is found valid and infringed, during the data protection term, the biosimilar applicant should not be permitted to market its product until expiry of the patent; and (6) BLA holders and patent owners in the biotechnology industry should have the choice, as they have in other industries, whether and when to assert their patent rights against infringers.

Identification of the relevant patents could be accomplished through a publication process, or it could be accomplished through a listing process similar to that required in the Hatch-Waxman provisions. There are a variety of special considerations in the biosimilars context. For example, it may not be possible at the time of BLA approval to identify all of the patents, particularly the process patents, that may be implicated by a biosimilar product 14 years later. To give another example, if the biosimilar applicant shares its application and describes its manufacturing process early in the data protection term, it will be important to ensure that the BLA holder and patents owners learn of subsequent changes made by the biosimilar applicant that might implicate patents not previously identified as relevant. In any case, the Hatch-Waxman provisions as they are currently drafted would not be suitable, for a variety of reasons. These include the fact that the listing requirement does not extend to process patents, the fact that 180-day generic exclusivity encourages poorly supported patent challenges a mere four years into the product's effective patent term; and the fact that the various incentive provisions (including the 180-day exclusivity and 30-month stay provisions) have resulted in expensive and distracting disputes over listability. As noted above, the present legislative discussion provides an opportunity for policymakers to draft patent resolution provisions that do not result in protracted private debates over which patents are actually relevant in the first instance.

V. 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?

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

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

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

These paragraphs respond to questions 1, 3, 4, and 5. In order to provide the incentives required to bring new biotechnology products to market, biosimilars legislation should include a substantial period of data protection, during which biosimilar applicants may not rely on safety and effectiveness data submitted by the innovator.

As explained above in response to questions 2 and 3 relating to patents, data protection and patents serve different purposes. Whether or not a patent is available, in order to bring a new invention to market, the sponsor must engage in a lengthy, expensive and commercially risky period of preclinical and clinical testing to generate the data needed for regulatory approval. The process typically takes 15 years and entails an investment of $1.2 billion or more, with no guarantee that the end product will reach the market, or recoup research and development costs if it does. A robust and certain period of protection for those data will ensure that innovators continue to bring new medicines to patients. Unlike market exclusivity (such as the seven years of market exclusivity available for orphan products), data protection protects the data and information owned by and submitted by an innovator to support the approval of its product. It does not preclude approval of a full application submitted by a competitor and is therefore not market exclusivity.

As also explained above, a substantial period of data protection is especially important for biotechnology products, because patent protection is often less robust than for small molecule drugs. Many biotechnology products are protected primarily by process patents or relatively narrowly drawn product patents that may be susceptible to work-arounds, especially under a regulatory regime for biosimilars that permits biosimilars to differ in their structural features from reference products. In short, while in the Hatch-Waxman setting the regulatory standard provides a helpful complement to patent protection, in a biosimilars setting the regulatory standard is likely to enable circumvention of patents that are already very narrowly drawn. Ideally,

therefore, the period of data protection for biotechnology innovators should equal the period of market exclusivity contemplated by Congress under the patent term restoration provisions of the Hatch-Waxman amendments, i.e., 14 years. (As explained below, this is also generally consistent with recent economic modeling suggesting that break-even lifetimes for new biological products ranges from 12.9 to 16.2 years.) In short, data protection and patents play different roles for biological products and small molecule drugs. If the data protection available for biotechnology innovators is less than the effective patent life available for small molecule drug innovators, it will skew investment options away from biotechnology and send the message that the United States no longer aims to be the world leader in biotechnology investment and innovation.

A mechanism for supplemental data protection is also essential, because the most important medical applications of biotechnology products are sometimes not discovered until many years after those products are initially approved. For example, alfa interferons were first approved in the 1980s for treatment of hairy cell leukemia and other cancers; it was not until the late 1990s that the products were found to be effective when used in combination with ribavirin for treatment of hepatitis C, a life-threatening disease for which no effective therapy previously existed. Another example is Remicade, which was first approved in 1998 for Crohn's disease. Eleven indications followed over the next nine years, including indications related to rheumatoid arthritis, colitis, and psoriasis. The core data protection period must be long enough to reward the initial burst of postmarket research and development common in this sector, but any biosimilars legislation should also provide an extension in the core period (e.g., an additional two years) if medically significant new uses are approved during a designated period following initial approval (e.g., eight years). This approach, similar to that adopted in Europe, would provide a more meaningful incentive for development of new indications than the supplemental data protection provided under the Hatch-Waxman amendments. The Hatch-Waxman provisions protect only the data supporting the new condition of use in question. This supplemental protection can be easily circumvented by off-label prescribing and dispensing. It might also be deemed appropriate to grant indication-specific data protection periods (comparable to the three-year periods granted for small-molecule drugs under the Hatch-Waxman amendments) for new uses that are approved after the initial data protection period expires.

Second generation products that incorporate changes in the molecular structure or other characteristics of earlier biological products — which are developed as new products, supported by extensive data, and marketed under new BLAs — should be entitled to their own period of data protection. These new products can offer therapeutic alternatives and improve patient care. For example, second generation vaccine products have yielded significant public health benefits. The first pertussis (whooping cough) vaccines were produced using whole cells of the infectious organism. Although these vaccines virtually eliminated a disease that had killed hundreds of children each year, they contained impurities that were capable of inducing serious adverse reactions. A second generation, acellular vaccine, developed after many years of research, largely

eliminated this risk without compromising efficacy. The same has been true for recombinant DNA-derived therapeutic protein products. For example, the first recombinant human growth hormone product differed by one amino acid from the structure of naturally occurring human growth hormone. Second generation products are identical in structure to natural growth hormone, thus ensuring that the product performs as similarly as possible to the natural substance.

In order to ensure incentives to develop these new and better products, policy makers should provide a new period of data protection for any product that is determined by FDA to require a full BLA. Healthcare providers and payors will then decide whether these products offer advantages over existing therapies, based on evidence from clinical trials and medical experience. This is the approach that has been taken in the European Union, where second generation biological products such as darbepoetin and pegylated interferon alfa have been accorded data protection. Moreover, it is plainly incorrect to refer to the marketing of second generation products as "evergreening." Once the data protection expires on a first generation product, biosimilar applicants are free to market their competing products. These follow-on versions of first generation products will obviously compete with the newer second generation products, but acceptance of second generation products in the marketplace (in lieu of cost competitive biosimilar first generation products) will depend on proving their benefits to healthcare providers, insurers, and others stakeholders.

Uncertainty about patent protection in this context makes data protection for second generation products even more essential. While the improvements that lead to second generation products may be patentable, a regulatory pathway that permits approval on the basis of similarity and an abbreviated data package may create strong incentives to circumvent the patents in question. In this situation, data protection will provide the only incentive to continue to innovate.

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?

We have not surveyed the economic literature regarding the minimum data protection term that will enable a robust industry for discovery and development of biologics. Modeling performed in 2007 by Professor Henry Grabowski of Duke University, however, demonstrated that the break-even lifetimes for new biological products ranged from 12.9 to 16.2 years. Henry Grabowski, Duke University Department of Economics Working Paper, "Data Exclusivity for New Biological Entities" (June 2007). Break-even occurs when the present value of net revenues equals the present value of research and development costs (or, equivalently, where a firm's risk-adjusted return on its research and development investment equals its cost of capital). The data protection term for approved products must also be sufficient to enable the sponsor to recoup the costs of developing failed products. Recent reports indicate that while

biological products may have a higher overall success rate in research and development than small molecule chemical drugs, they have lower success rates in the most expensive (Phase III) trials — indicating that biological products that fail in clinical trials often do so only after very high developments costs have been incurred. (Id., citing a study by Goldman-Sachs, as well as another paper by DiMasi & Grabowski from 2007.) In addition, biological products often require a much larger manufacturing investment that has to be committed to earlier in the product development life-cycle. This may necessitate additional data protection beyond the break-even point identified by Professor Grabowski.

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

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?

This paragraph responds to questions 6 and 7. As explained above, patents and data protection serve different roles, and neither can substitute for the other. To ensure continuing invention of biological molecules and manufacturing processes, and to ensure continuing investment in the research and development of safe and effective medicines resulting from those inventions, both patent protection and robust data protection must be made available. As stated above, if policymakers do not provide a substantial period of data protection for biotechnology-derived medicines or if the period is less than the optimal effective patent life found in the Hatch-Waxman amendments for small molecule drugs (14 years), then they will skew investment decisions away from biotechnology and risk sending the message that the U.S. no longer aims to be the world leader in biotechnology investment and innovation.

VI. Economic Impact

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

We have not projected the cost savings that would be achieved through enactment of a biosimilars pathway or the time period during which these savings could be realized. Although savings would be created, many factors need to be taken into account. For example, in our extensive experience manufacturing both small molecule drugs and biological products, the manufacture of biological products is far more complicated and more expensive. It also requires many more years to establish biological

product manufacturing facilities than to establish facilities for the manufacture of small molecule drugs. In addition, unlike generic small molecule drugs, biosimilars will require premarket analytical, preclinical, and clinical work, and experience in Europe (and thus far in the United States, with Omnitrope) suggests the applications will be extensive and therefore expensive to compile. Moreover, because of immunogenicity and other safety concerns, biosimilars will require postmarket surveillance and possibly antibody testing. The cost of these postmarket commitments must be taken into account. Further, biosimilar manufacturers may face costs associated with marketing their products. Experience in the small molecule setting also suggests that significant price reductions will not occur without a field of multiple biosimilar competitors for each innovator product, and particularly because of the complexity of these products, we believe it could be some time before this occurs. Finally, although the coverage of patents is less certain in this setting, it is possible that patents will prevent innovative biologics from being eligible for copying in the near term. Thus, while we suggest the committee turn to other stakeholders for specific projections of cost savings and time horizons, we advise close scrutiny of all assumptions on which projections are based as well as caution regarding overly optimistic projections.

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?

At Johnson & Johnson, we embrace research and science - bringing innovative ideas, products and services to advance the health and well-being of people. The combination of an increasingly complex external environment coupled with demand for innovative, cost-effective medicines drives us to make focused choices on how to invest our resources. As one of the world's preeminent sources of biopharmaceutical medicines, we understand that we must maintain a culture focused on innovation in pursuing scientific leads that have the potential to revolutionize patient care. Our scientific capabilities include state-of-the-art discovery and global development, world-class manufacturing of biologics and strong commercialization entities in more than 175 countries. Biologics offer the ability to directly address new mechanisms or new disease pathways, they often have the ability to target diseases with high unmet need, and they hold the potential of delivering breakthrough outcomes to patients. But as we continue our work to uncover the promise of new and innovative biologic therapies for patients for generations to come, it is critical that appropriate incentives for innovation are maintained.

We have not projected the cost savings that would be achieved through enactment of a biosimilars path, and the actual cost of individual reference products and biosimilars will vary. The price differential is unlikely to be as significant as it is in the small molecule setting, where price reductions are driven by the limited investment required of generic companies and the large field of generic competitors. Biologics manufacturing facilities require a substantial investment of resources, and biosimilars are

likely to be supported by extensive preclinical and clinical data packages that also require substantial investments. These factors will in turn reduce the field of competitors to one much smaller than that faced by small molecule manufacturers.

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

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?

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?

This paragraph responds to questions 3, 4, and 5. The United States is currently the undisputed world leader in biotechnology, including the research and development of new biotechnology-derived medicines. Our success is attributable to many factors, but a key element has been the investment and commercial risk-taking of private industry, which is primarily responsible for the research and development that brings most new products to patients. The willingness and ability of private industry to make the investments necessary for this research and development depend on the existence of predictable regimes that provide appropriate incentives for investment and protection for that investment. In addition to a predictable patent regime, a substantial data protection period is essential for the continued robust investment in the discovery and development of new biological products. The European Union is keenly aware of the importance of encouraging development of its biotechnology sector. The EU regulatory regime for "similar biological medicinal products," described in the next section, is part of a comprehensive program to encourage investment in biotechnology. If the data protection and patent provisions in U.S. biosimilars legislation are not more robust than those in Europe, we will risk ceding our leadership in this sector.

VII. <u>European Model</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.?

Yes. The EU has shown that such guidance can be developed through open and transparent procedures. This process ensures that all relevant information (including experience with process changes for innovative products and academic

research on issues such as immunogenicity) is fully considered, rather than relying solely on information available to regulators and biosimilar applicants. The process also has the advantage of providing a detailed, public pathway for biosimilar manufacturers, so that all companies wishing to enter the field know the ground rules and information is not confined to a small number of biosimilar insiders.

The EU experience has also shown that product-specific guidance can be developed reasonably promptly, usually within 12 to 18 months. If similar guidance procedures are followed in the United States and are initiated during the data protection period for innovative products, there is no reason why final guidance cannot be issued in time for biosimilars to be approved when data protection periods expire.

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?

A very strong case can be made that a 14-year data protection term — rather than the 5 years available for small molecule drugs or the 10 years available in the European Union — is appropriate in a scheme for approval of biosimilars. First, as noted above, the European Union is keenly aware of the importance of encouraging development of its biotechnology sector. The EU regulatory regime for "similar biological medicinal products" is part of a comprehensive program to encourage investment in biotechnology. If the data protection and patent provisions in U.S. biosimilars legislation are not more robust than those in Europe, we risk ceding our leadership in this sector. Second, as discussed above, in the United States patents alone are unlikely to provide the certainty and predictability required for investments needed to bring new biotechnology products to patients. While in the Hatch-Waxman setting the regulatory standard provides a helpful complement to patent protection, in a biosimilars setting the regulatory standard is likely to enable circumvention of patents that are already very narrowly drawn. Ideally, therefore, the period of data protection for biotechnology innovators should equal the period of market exclusivity contemplated by Congress under the patent term restoration provisions of the Hatch-Waxman amendments, i.e., 14 years. A key House Report from the Hatch-Waxman amendments indicates that Congress selected 14 years so that "research intensive companies will have the necessary incentive to increase their research and development activities." H.R. Rep. No. 98-857, at 41 (1984).

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

The United States is currently the world leader in biotechnology, but the European Union has deep resources in the sector and is actively pursuing initiatives designed to close the gap. Even developing countries such as India and Korea have the potential to become serious competitors. Any U.S. legislative regime for biosimilars will send an important signal to biotechnology manufacturers throughout the world. A regime that undermines innovators' intellectual property rights or does not afford an appropriate period of data protection will send the message that the United States is not seeking to maintain its leadership position in biotechnology.

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 model is by far the most important to study, because it is the most carefully considered biosimilars regime among developed countries. European regulators now have years of experience considering the analytical, preclinical, clinical, and postmarket issues for a number of key product classes, as well as experience both approving and rejecting products. Key elements of the EU model include: (1) a science-based system that puts patient safety ahead of all other considerations, drawing on the collective knowledge of expert committees and national regulatory authorities from the entire European Union; (2) public proceedings to develop data requirements; (3) requirements for clinical testing; (4) special emphasis on immunogenicity testing, both before and after approval of biosimilars; (5) recognition that biosimilars are not to be regarded as generic drugs; and (6) incentives for research and development, including substantial periods of data protection and maintenance of innovators' rights under the patent system.

Although the European system is instructive in these respects, it cannot be transferred verbatim to the U.S. legal and political environment. For example, the primary legislation on which the EU system relies is, by U.S. standards, very succinct. This is partly because the European Commission, which drafts the legislation, is also responsible for approving biotechnology products. The guidance documents that are key to the European approval system were actually under development before the legislation was adopted, and all parties knew how the process would work. Under the U.S. system of separation of powers, Congress must provide more specific instructions to FDA if it wishes to achieve a result similar to that in the EU. It is for this reason that most provisions of U.S. drug law enacted in recent years (including the FDAAA) are far more prescriptive than their counterparts in Europe. Action-forcing mechanisms and dedicated funding may also be necessary to ensure that FDA has the incentive and resources to develop guidance documents in consultation with relevant stakeholders. A new advisory committee may be appropriate to provide the kind of independent expert advice that the

European Medicines Agency (EMEA) receives from its committees and working parties and national authorities around the EU.

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?

Only a small number of biosimilars have been approved in Europe and the United States, and actual clinical experience in the market is minimal. It is worth noting, however, that the European Medicines Agency refused to approve one biosimilar (an alfa interferon) due to safety and effectiveness issues that were only detected because comparative clinical trials were required.