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The Honorable Frank Pallone
Chairman
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Nathan Deal
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Pallone and Ranking Member Deal:

Thank you for providing Amgen with the opportunity to participate in the stakeholder discussion regarding biosimilars. As one of the world's first biotechnology companies, we believe we can offer a unique and valuable perspective on what is required to develop and manufacture safe and effective biologic drugs. We appreciate this opportunity to work with the Committee as it grapples with the complex questions surrounding the establishment of a legislative framework for biosimilars (also known as "follow-on biologics").

Amgen discovers, develops, manufactures and delivers innovative human therapeutics. A biotechnology pioneer since 1980, Amgen was one of the first companies to realize the new science's promise by bringing safe and effective medicines from lab, to manufacturing plant, to patient. Amgen therapeutics have changed the practice of medicine, helping millions of people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, and other serious illnesses. With a deep and broad pipeline of potential new medicines, Amgen remains committed to advancing science to dramatically improve people's lives.

In 2007, Amgen invested 3.2 billion dollars in research and development of new medicines, and we focus those research and development efforts on novel therapeutics for the treatment of grievous illness. Our innovations have helped millions of people worldwide who suffer from medical conditions for which there are few effective treatments. It is from this perspective that we submit our answers to the thoughtful questions posed by the Committee.

Please feel free to contact us should you require any additional information regarding the information described in these responses. We look forward to continuing this constructive dialogue and appreciate your leadership on this important issue.

Sincerely,

David Beier
Senior Vice President,
Global Government Affairs

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

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

Amgen Executive Summary

An abbreviated approval pathway for biosimilar products (also referred to as "follow-on biologics" or "FOBs") that limits the risk to patients can, and should, be developed. However, that pathway must be tailored to address the unique characteristics of biotechnology. If not, patient safety and future medical innovation will be compromised. Biological products differ from small molecule drugs (traditional, chemical medicines) in their size, complexity, structure, and method of manufacture. These differences have profound implications for both the requirements of the regulatory pathway and the ways that pathway will foster or discourage future innovation.

Biosimilars are not identical to innovator products. Their safety profiles can also differ.
Biologics are manufactured from living cells or organisms by programming a cell line to produce a desired protein in a highly controlled environment. The manufacturing process for each biologic largely defines the clinical properties of the resulting biologic product. The end product is a highly complex, heterogeneous mixture that, for the most part, cannot be fully characterized with today's science. Small differences in manufacturing processes can cause significant differences in the end product. *No two biologics made using different cell lines or a different manufacturing process will be the same.*

A *biosimilar* version will be manufactured using a different cell line and process from that of the innovator biologic. Due to the innate complexity of biologics, this will inevitably lead to differences between the structures of the biosimilar and the innovator product that could have significant clinical implications for patients. A biosimilar product could be more or less potent than the product it is imitating, or it could cause an immune response ("immunogenicity") not seen with the innovator product.

Pre-approval clinical testing for safety, efficacy and immune response is essential.
Healthcare professionals and patients must have confidence that any biosimilar approved for marketing in the United States will have a similar safety, efficacy, and immunogenic potential as the innovator in each and every approved indication. In other words, it should not be possible to detect any clinically meaningful difference between the biosimilar and the innovator biologic. It is therefore logical for any statute to require that the safety, efficacy and immunogenic potential of the biosimilar are all similar to those of the innovator product, in all indications for which approval is being sought, *i.e.* these characteristics of the biosimilar must be no worse than the innovator. *Meeting this standard will necessarily require that clinical studies are conducted prior to approval to demonstrate that there are no clinically meaningful differences between the biosimilar and the innovator.*

Immunogenicity is a special safety concern for all biologics because the body may identify these large molecules as foreign. Scientists do not yet have sufficient knowledge about the human immune system to be able to predict whether a certain biologic – or the differences observed between an innovator biologic and a biosimilar – will cause the body to mount an immune response. It is scientifically *incorrect* to assume that a biosimilar will have a similar immunogenic potential simply because it is structurally similar to the innovator. There will inevitably be differences between the innovator and the biosimilar, and the only way to understand the immunogenic potential of any biosimilar is to assess it in patients through clinical testing. *In the interest of ensuring patient safety, it is therefore essential that immunogenicity testing prior to approval of any biosimilar be mandated by statute.*

In addition, all biologics must be clinically tested for immunogenicity *after* approval for marketing to continue to detect any immune response. Post market surveillance can only be effective if every biologic is identified by manufacturer in order to facilitate determining which product is the source of the immune response. Unique INNs (International Nonproprietary Names) for all biological products are the optimal means of achieving universal identification and clear manufacturing provenance.

Public process for approval standards creates confidence among patients and physicians. FDA should have the discretion to determine the extent of clinical testing necessary for approval of a biosimilar, using a transparent public process that utilizes both its internal expertise and that of the external scientific and medical communities to inform their view. The complex scientific issues raised by biosimilars make it essential that all scientific experts have an opportunity to weigh in on appropriate approval standards. Furthermore, by developing and publishing formal product class-specific guidance documents, FDA would be able to ensure consistency in the approval standard within each product class.

Historical experience is not predictive of testing requirements for biosimilars.
FDA's experience with manufacturing changes made by the innovator could be used to inform the testing requirements for biosimilars; it cannot, in and of itself, be used as a point of reference for determining the testing requirements necessary to approve a biosimilar product. The vast majority of manufacturing process changes proposed by an innovator do not impact product structure. However, by definition, the process used to manufacture a biosimilar will incorporate a biological portion—the part of the process involving living organisms—that differs in meaningful ways from that of the innovator. As such, any biosimilar manufacturing process will include at its core such important differences to the innovator's process that structural changes to the biologic and differences in the product's impurity profile are expected. This leads inevitably to a requirement for clinical studies to establish an absence of clinically meaningful differences between the innovator biologic and the biosimilar.

Automatic Substitution by pharmacists would compromise patient safety.
Due to the potential for immunogenicity and the attendant need for careful post market surveillance of biotech products , *substitution at the pharmacy level — without the consent of the physician — is not appropriate in the biotech context.* Biosimilars will not be identical to the reference product they attempt to copy and will be approved based on different clinical data than the innovator biologic. This being the case, only a physician with an in-depth knowledge of the patient's history can prudently choose to prescribe a specific biologic — whether biosimilar or innovator – that the physician deems appropriate for an individual patient. Additionally, it will be very difficult to trace adverse events to a particular product if substitution occurs repeatedly and without the physician's involvement. Notably, the practice of biologic substitution by the pharmacist without the physician's consent has been rejected in more than half of the EU member states (including France, Germany, the United Kingdom, Italy and Spain).

The future of biotech medicines depend upon continued incentives for innovation.
A model for approving biosimilars must include adequate protections for the innovators that provide incentives for continued innovation or future cures may never materialize. The incentive structure provided by the Hatch-Waxman generic drug model is too complicated, has resulted in a vast increase in litigation, is inapplicable to products that are "similar" rather than "identical," and fails to provide adequate protections for biotech innovators. A model with sufficient incentives for ongoing biotech innovation would address both the timely resolution of patents disputes and adequate protection for the data developed to secure FDA approval of the innovator's product. First, an abbreviated approval model for biosimilars must include a mechanism for facilitating resolution of patent disputes before a biosimilar product comes to market. Second, the data developed over many years and at great expense to the innovator must be protected from use by others for a period of time in order to give the innovator an opportunity to recover the investment. A period of 14 years of data exclusivity is appropriate and will encourage future innovation.

The approval pathway for biosimilars will have both commercial and therapeutic consequences.
When assessing the potential for cost-savings of biosimilars, the difference in the science of biotechnology and of traditional pharmaceuticals is a crucial variable. The market dynamic and any associated savings from biosimilars is likely to be far different from the generic model, which consists of

heavy discounting and rapid uptake of generics. According to highly credible analyses, savings estimates for biosimilars are modest over a ten-year time period when compared to the traditional generic model.

Any calculation of the economics of biotech medicines should include the contributions of the biotech industry to the U.S. economy and to the wellbeing of patients. The U.S. leads the world in biotech research and innovation. It would be short sighted to undermine this productive, but fledgling industry when the U.S. is losing jobs to overseas competitors – and while millions of patients are still waiting for cures,

Finally, responsible legislation implementing an abbreviated approval pathway for biosimilars should be driven as much by patient safety and outcomes as by economics. In fact, the two are closely intertwined, since the commercial health of the biotech industry has a direct impact on the health and productivity of the patient population. *Without incentives to invest in innovation, the R&D pipeline of breakthrough therapies will be diminished and patient outcomes will be affected.* Beyond the human costs from chronic disease, the demise of innovation will have significant financial costs in terms of the lost work and productivity of patients.

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?***

Biologics are different from traditional "small-molecule" chemical medicines administered in pill form in that they are large enough to stimulate the body to mount an immune response (*i.e.* produce antibodies) by themselves. Unlike biologics, chemical medicines are too small to be recognized by the immune system without first binding to a patient's own protein, possibly to one of the many proteins circulating in the blood stream – this can result in rare short-term reactions like allergy or hypersensitivity reactions. Once levels of the chemical medicine in the body have decreased, usually in a matter of hours, the immune response will disappear and will no longer harm a patient unless the chemical medicine is administered again. Conversely, once the immune response against a biologic has started, particularly against biologics that resemble the patient's own proteins, the immune response can persist, sometimes years after the biologic has stopped being administered. It is the potential to create a sustained immune response to a patient's own protein and block important biochemical pathways for long periods of time that makes immunogenicity of biologics a special safety concern compared to chemical medicines.

Immunogenicity occurs when the human body encounters a protein that it recognizes as "foreign." Biologics are often recognized as "foreign" by the body's immune system; when this happens, a series of events – an "immune response" – can be triggered to "fight off" the foreign protein. The nature of this immune response can vary from being clinically benign (*i.e.*, the antibodies have no apparent effect) to severe, for example when the body produces specific antibodies that are capable of binding to, and eventually destroying, the foreign protein. In the case of invading micro-organisms or when vaccines against diseases like diphtheria or tetanus are administered to patients, the body's immune response is very helpful and protective. In the case of biologics like insulin or growth hormone, however, an immune response from the body is unwanted. If the body's immune system recognizes the biologic and this response leads to a change in the biologic's efficacy, or destruction of the biologic, patients could lose the beneficial effect that the biologic was intended to provide.

In some rare cases, this type of immune response to a biologic will cause the body to produce antibodies that attack not only the biologic administered to the patient, but also the protein normally produced by the body. For example, Eprex® (epoetin alfa) is a biologic that is marketed in Europe to treat anemia in certain patients who, for example, are deficient in the production of erythropoietin, a protein naturally produced by the body that is essential for production of red blood cells. Following a series of minor manufacturing changes several years ago, many patients in Europe developed an immune response against Eprex®. The antibodies produced in the immune response by these patients not only blocked the ability of Eprex® to stimulate the production of red blood cells, but also blocked the patients' own erythropoietin from doing so. The consequences of this immune response were so severe that many patients were no longer able to produce their own red blood cells.[1]

[1] N. Casadevall et al., "Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin," New England Journal of Medicine, Vol. 346 No. 7 (Feb. 14, 2002) at pp. 469-475.

Immune responses to biologics vary by the type of biologic and the disease state of the patient population to be treated with the biologic, and they are unpredictable in terms of whether or not a particular patient will mount an immune response. Some biologics are more likely to trigger an immune response in patients than other biologics and we do not have a precise understanding of exactly what characteristics of the protein lead to such immune responses – minor, subtle or even undetectable changes in the protein structure could lead to an immune response, and so this is not something that can simply be tested for in the laboratory. And depending on the particular biologic, the consequences of the body developing an immune response may be more or less severe. However, it is not possible to predict the likelihood of a patient developing an unwanted immune response, nor is it possible to predict the characteristics of the immune response, or the clinical consequences and significance of such immunogenicity.

It is therefore scientifically incorrect to assume that a biosimilar that is intended to be structurally similar to the innovator biologic will have similar immunogenic potential. Scientists expect there to be structural differences between the biosimilar and the innovator biologic, and it is not possible at this point in time to determine or even predict whether these differences will (or will not) cause any differences in immune response caused by the biosimilar versus the innovator.

Scientists are still developing an understanding as to why some therapeutic proteins are more likely to induce an immune response. At this time, it is unknown which changes in a biologic might cause the body to recognize it as a "foreign protein" and trigger an immune response – so the immunogenic potential of any biologic medicine can only be assessed in appropriate clinical studies.

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?***

Immunogenicity is a characteristic of each particular biologic, not of a class of biologics. It is therefore very important that immunogenicity testing be performed for all biologics – innovator or biosimilar – prior to approval.

A biosimilar will be manufactured using a process that is different from that of the innovator biologic, and this will inevitably lead to a range of differences in the structures of any given biosimilar and the innovator product. In addition, the impurity profile of the innovator product and the biosimilar will also likely be different. These impurities can also contribute to an immune response to a protein therapeutic. This expectation of differences has already been recognized by the European Medicines Agency (EMEA) in its guidelines for biosimilars and by the World Health Organization in its draft guideline on subsequent entry biological medicinal products:

"It is not expected that the quality attributes in the similar biological and reference medicinal products will be identical."[2]

"The structure of biotherapeutic is also very sensitive to various production parameters so that it is highly unlikely that one manufacturer can reproduce in fine detail, the biotherapeutic manufactured by another company."[3]

Indeed, this appears to be the case with recently approved biosimilars in Europe and with the approval of Omnitrope® (somatropin recombinant) in the United States. The European Public Assessment Report (EPAR), which describes the EU regulators' findings in approving products for a biosimilar version of Eprex® (epoetin alfa) describes the following differences found between the reference product and the proposed biosimilar:

EMEA EPAR for Sandoz Biosimilar Epoetin Alfa[4]

- "Differences were observed at the glycosylation level"
- "Phosphorylated high mannose type structures… were detected at higher levels than in Eprex"
- "[L]ower values on N-glycolyl-neuraminic acid and diacetylated neuraminic acids as compared to Eprex"
- "Peptide maps show some differences … in the O-linked glycan due to a higher sialylation and… tends to have lower content of the oxidized variant"

Likewise, the U.S. Food and Drug Administration (FDA) noted the following differences between the reference product, Genotropin® (somatropin recombinant) and the proposed biosimilar, which was ultimately approved as Omnitrope®:

FDA Chemistry Review for Omnitrope®[5]

- "The results of this study … demonstrate that BC rhGH [Omnitrope] produced at full scale is comparable to Genotropin"
- "The impurity profile of the Omnitrope drug product shares some similarity with Genotropin; however, the profiles are not identical"
- "[*redacted*] impurities [*redacted*] are present in the Omnitrope batches and are not in any Genotropin batches"
- "Additionally, there appears to be a higher level of deamidated variants in the Omnitrope samples"

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[2] European Medicines Agency, "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues," EMEA/CHMP/BWP/49348/2005 (Feb. 22, 2006), at p. 5, available at http://www.who.int/medicines/services/inn/innquidance/en/index.html (last visited April 17, 2008).
[3] "WHO Guideline on Licensing Approaches for Subsequent Entry Biological Medicinal Products (DRAFT)" (April 15, 2008), at p. 3.
[4] European Medicines Agency, "European Public Assessment Report for Sandoz biosimilar epoetin alfa, Scientific Discussion" (Aug. 28, 2007), at pp. 2-3, available at http://www.emea.europa.eu/humandocs/Humans/EPAR/binocrit/binocrit.htm (last visited April 18, 2008).
[5] U.S. Food and Drug Administration, "Chemistry Review for Sandoz somatropin recombinant (Omnitrope)," available at http://www.fda.gov/cder/foi/nda/2006/021426s000_ChemR.pdf (last visited 4/29/2008).

In the context of the magnitude and type of differences observed between biosimilar and innovator products, scientists do not yet have sufficient knowledge about the human immune system to be able to predict whether a certain biologic – or the differences observed between an innovator biologic and a biosimilar – will cause the body to mount an immune response. The only way to understand the immunogenic potential of any biosimilar is to assess it in patients by way of clinical testing.

The immunogenic potential of any protein is dependent on multiple factors, including its basic linear sequence, how it folds into a three-dimensional structure, its tendency to associate into large aggregates ("clumps"), and impurities that co-exist in the product. All of these factors can affect how the immune system recognizes a protein, and all should be monitored during manufacture; however, analytical techniques are not sensitive enough to detect all relevant changes that can occur, or to predict whether the human immune system will detect them. Animal models also are of limited usefulness: because the precise structure of proteins is usually different between species, studies in animals cannot reliably predict the immunogenic potential of biologics intended for use in humans.

In the case of Omnitrope®, contamination of the product with host-cell protein was not predicted by the analytical or animal studies to cause an immunogenicity problem. However, after initiating clinical studies, a high (57%) immunogenicity rate was observed in a small clinical trial of 89 children who were administered Omnitrope®, compared to a normal immunogenicity rate of 2% in patients who received the innovator biologic, Genotropin®.[6] In this case, it proved to be bits of the cell used to make Omnitrope® (*i.e.* an impurity) that stimulated the body to mount this immune response, rather than the protein itself. Fortunately, because this high immunogenicity rate was discovered in the clinical trial, the manufacturer was able to reconfigure its process and re-do its clinical study, to get the immunogenicity rate at a level closer to the innovator.

Clearly, it is far better to discover this type of immune-mediated problem sooner – in the context of a controlled clinical trial – than later, after a biologic product has been introduced into the marketplace.

In the interest of ensuring patient safety, it is therefore essential that immunogenicity testing prior to approval of any biosimilar be mandated by statute. This is the standard established by the European Medicines Agency in its guidelines for biosimilars and by the World Health Organization in its draft guideline on subsequent entry biological medicinal products:

> "The immunogenicity of a similar biological medicinal product must always be investigated."[7]

[6] See European Medicines Agency, "European Public Assessment Report for Omnitrope, Scientific Discussion," (April 12, 2006) at p. 24.http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en6.pdf (last visited April 18, 2008).

[7] European Medicines Agency, "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues," EMEA/CHMP/BWP/49348/2005 (Feb. 22, 2006), at p. 7, available at http://www.who.int/medicines/services/inn/innquidance/en/index.html (last visited April 17, 2008).

"Immunogenicity of a biological medicinal product should always be investigated pre-authorization."[8]

In requiring immunogenicity testing both before and after approval, the statute should set the expectation that the immunogenic potential of a biosimilar is similar to, or no worse than, that of the innovator. It is clearly unacceptable for a biosimilar to have a worse immunogenicity profile, or to pose greater risks to patients, than the innovator – by definition, such a product would not be similar to the innovator.

The FDA possesses the requisite knowledge and expertise to ensure that this statutory expectation is met. The agency has the means to evaluate the type of biologic and the disease state of the patient population that would be treated with the biosimilar, as well as the complement of available non-clinical and clinical testing, to establish the amount and number of clinical trials that should be required under this statutory requirement for any particular biologic product or class of biologic.

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?***

It is important to correctly understand the difference between development of a biosimilar product and a manufacturing process change introduced by an innovator with respect to an approved biologic. The U.S. Food and Drug Administration (FDA) and other regulatory agencies around the world have recognized that they differ to such an extent that it is inappropriate to directly apply any current legislation or regulatory practice that controls manufacturing process changes, to the legislative and regulatory standards that will be necessary for the approval of biosimilars.

The vast majority of manufacturing process changes proposed by an innovator do not impact product structure or impurity profile. These simple changes – such as changes to equipment that do not have contact with the protein or changes to test methods – are easy to evaluate with purely analytical approaches, and no immunogenicity testing is necessary. However, when there are significant changes to the *biological* portion of the manufacturing process – that portion involving living organisms – a shift in the product profile is more likely. The innovator will make every effort to minimize the scope of these shifts, but some differences may remain: in these cases, immunogenicity testing may be necessary.

Indeed, experience with innovator biologics has been that significant changes to the biological portions of manufacturing processes have required non-clinical and clinical studies. Furthermore, on several occasions minor shifts in the product profile have had clinical effects that could not have been anticipated from purely biochemical evaluations of the molecule or by non-clinical (animal) studies.

[8] "WHO Guideline on Licensing Approaches for Subsequent Entry Biological Medicinal Products (DRAFT)" at p. 36 (April 15, 2008).

Accordingly, FDA has appropriately exercised its discretion whether to require immunogenicity testing for specific manufacturing changes.

By definition, the process used to manufacture a biosimilar will incorporate a biological portion that differs significantly from that of the innovator. A biosimilar manufacturer will have, among multiple other differences from the innovator, a different manufacturing site, different equipment, a different cell-line, different cell culture/fermentation conditions, different purification procedures, and a different formulation. As such, any biosimilar manufacturing process will include at its core a type of process change of such magnitude that, if introduced by an innovator, would lead to structural changes to the biologic, differences in the product's impurity profile and – inevitably – to a requirement for clinical studies and immunogenicity testing.

For these reasons, it would be scientifically inappropriate to apply historical experience of FDA decisions regarding manufacturing process changes to the creation of a legal pathway for approval of biosimilars. Structural and impurity profile differences between a biosimilar and the innovator are expected. The immune system is exquisitely sensitive and unpredictable in its ability to react to such differences – including differences that may not be detectable using state-of-the-art analytical techniques. As has been required in Europe and recommended by the World Health Organization, immunogenicity testing of biosimilars must always be conducted prior to approval.

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?***

It is imperative that healthcare professionals and patients have confidence that any biosimilar approved for marketing will have a similar safety, efficacy, and immunogenic potential as the innovator in each and every approved indication. In other words, it should not be possible to detect any clinically meaningful difference between the biosimilar and the innovator biologic.

When it comes to establishing a legal pathway for the approval of biosimilars, it is therefore logical for any statute to require that the safety, efficacy and immunogenic potential of the biosimilar are all similar to those of the innovator product, in all indications for which approval is being sought, *i.e.* these characteristics of the biosimilar must be no worse than the innovator.

Meeting this standard will necessarily require that clinical studies are conducted to demonstrate that there are no clinically meaningful differences between the biosimilar and the innovator. This is because safety, efficacy, and particularly immunogenicity cannot be reliably evaluated or predicted without clinical data.

Extrapolating evidence of efficacy, safety and/or immunogenicity for one indication to other indications of the innovator biologic poses a number of important scientific and medical challenges that must be carefully considered:

1. By definition, extrapolation of efficacy, safety and immunogenicity from one indication to another requires a demonstration of the similarity of these characteristics in one indication of the innovator biologic. Such a standard can only be met by the conduct of

appropriately designed and conducted comparative clinical study(ies) that reliably establish the absence of clinically meaningful differences from the innovator.

2. The degree of similarity established in the above indication would have to be sufficiently certain that seemingly minor differences in one indication are not exaggerated in another. For example, a minor difference in potency may be clinically meaningless in one indication, but in other indications, where the dose of the biologic is higher or the patients more sensitive, this difference may be amplified to the extent that it becomes a safety concern.

3. There may be certain risks that cannot be evaluated in just one indication. For example, immunogenicity can only be evaluated in patients who have a fully functioning immune system. If the efficacy, safety and immunogenicity are studied in cancer patients receiving chemotherapy, that chemotherapy can often suppress the immune system to the extent that even a highly immunogenic protein will not be recognized. In this case, extrapolation to non-cancer indications, where patients have a fully functioning immune system, would not be possible and further clinical data in that patient population would be necessary before approving the biosimilar for that indication.

4. Extrapolating evidence from one indication to other indications would also involve considering the benefits or, more specifically, the risks for patients themselves. Extrapolation, by definition, makes the assumption that the efficacy, safety and immunogenicity will be the same. In certain cases, were this assumption to prove incorrect, the consequences for the patient could be immediately identifiable and correctable. In other cases, however, the consequences for the patient of lack of efficacy or an unexpected safety issue may not be correctable or may indeed be fatal.

Extrapolation of indications should therefore not be a "foregone conclusion." By its very nature, such extrapolation requires in the first instance, complete and reliable evidence of similar efficacy, safety and immunogenicity in at least one indication for which the innovator biologic is approved.

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 Food & Drug Administration Amendments Act of 2007 (FDAAA) provided the U.S. Food and Drug Administration (FDA) with a host of enhanced post-market authorities, including the authority to require post-market studies or clinical trials, to request labeling changes to reflect new safety information, and/or to require a sponsor or applicant to submit and execute a Risk Evaluation and Mitigation Strategy (REMS).

Given that a biosimilar will likely be approved based on a more limited data set than the innovative product and that, by definition, a biosimilar will not fulfill an unmet medical need,

there is an even greater need to continue to evaluate the product in the post-approval setting. The European Medicines Agency has stated:

> It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.[9]

In addition to requiring such a commitment to post-marketing surveillance as a condition of approval, any statute should provide FDA with the full panoply of authorities provided in FDAAA, to ensure the ongoing safety of biosimilars once they have been introduced into the market. European regulators have recognized this by requiring biosimilar applicants to submit a risk management plan that details the risk mitigation activities that must be undertaken, in agreement with the authorities, after regulatory approval of a biosimilar.[10]

Biosimilars are unique products, and should be held to the same high standards of safety, purity, and potency as innovator biologics. Any biosimilar legislation should ensure that FDA's post-market authorities apply to biosimilars. FDA should be permitted discretion in determining the specific situations in which a biosimilar applicant may be required to conduct post-market studies, or to fulfill some other post-market requirement that may be different from that required for the reference product. To the extent that the pre-approval requirements for a particular biosimilar were not as extensive as that required for the innovator reference product, it may be necessary for FDA to subject that biosimilar to more rigorous scrutiny and application of the agency's post-market authorities to further protect patient safety. Notably, however, in no case should the application of FDA's enhanced post-market authorities to biosimilars be permitted to substitute for the pre-approval requirements necessary to ensure their safety and effectiveness.

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?***

When discussing non-proprietary naming for biologics, it important to consider why this question is being debated in the United States and other jurisdictions. In any health system, it is essential that physicians, patients, and drug safety authorities are able to distinguish between "similar" biologic medicines that are made by different manufacturers, in order to ensure robust

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[9] European Medicines Agency, "CHMP Guideline on Similar Biological Medicinal Products" (CHMP/437/04) (Oct. 30, 2005), at p. 4, available at http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf (last visited April 29, 2008).

[10] See, e.g., Section 4.3, "Clinical Safety & Pharmacovigilance Requirements," in "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues," EMEA/CHMP/BMWP/42832/2005 (Feb. 22, 2006).

pharmacovigilance and to prevent inappropriate switching of medicines. Requiring by statute that all biologics – biosimilar or innovator – are assigned distinct non-proprietary names would be a simple and effective means of achieving this important public health goal.

Biologic medicines need to be identifiable by name and manufacturer to effectively track safety concerns that arise after product approval. In the case of serious adverse events, public health officials need to be able to attribute the adverse event to the specific product – by manufacturer – in order to determine the root cause of the safety concern. Moreover, if an adverse event is mainly associated with only one biologic medicine in a class, public health authorities will need to be able to link the safety problem with the specific product, in order to identify the patients to whom that particular biologic (and not another in the class) was dispensed.

Without a distinct name for each biologic medicine produced by different manufacturers, a significant number of safety reports would not link the reported adverse event with the specific manufacturer of the medicine, rendering the pharmacovigilance system for biologic medicines ineffective. Even in pharmacies that retain information about the manufacturer of the product dispensed as a matter of practice, incomplete information and human error commonly thwart these policies.

Some drug safety reporting requirements and structures permit reporting of drug-associated adverse events by product name (International Nonproprietary Name, or "INN"). The World Health Organization (WHO) has stated:

> "The existence of an international nomenclature for pharmaceutical substances, in the form of INN, is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide."[11]

Assigning different INNs to biologics that are made by different manufacturers would ensure that safety reports make reference to the correct product. In the absence of such action by the WHO, options for establishing unique non-proprietary names as designated by the United States Adopted Names Council should be explored.

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?***

It is essential for the innovator and the biosimilar to have the same mechanism of action. If they were permitted to have different mechanisms of action, then it would be a logical conclusion that they will have a different biological effect and therefore differences in safety, efficacy, and immunogenicity. It would be illogical for a biosimilar, which by definition the manufacturer is attempting to make similar to the innovator biologic, to have a different mechanism of action.

[11] World Health Organization, "Guidance on International Nonproprietary Names," available at http://www.who.int/medicines/services/inn/innquidance/en/index.html (last visited April 17, 2008).

However, there are innovator biologics – and certain indications for innovator biologics – where the precise mechanism of action is not completely understood. Under these circumstances, the biosimilar applicant should not be obligated to determine that mechanism of action, provided that clinical studies have been conducted and confirmed the absence of clinically meaningful differences in the safety, efficacy and immunogenicity between the innovator biologic and the biosimilar.

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 difficult to speak in generalities about the levels of batch-to-batch variability in a biologics manufacturing process. Some processes will have more variability, others will have less. What can be stated is that for an innovator's biologic, the batch-to-batch variability will be controlled within ranges that are grounded in, and justified by, the clinical experience gained with that product. Specifications and controls that would permit a significant departure from such experience are not tolerated by regulatory agencies. In addition, the relative level of batch-to-batch variability will often decrease with time and experience, as the innovator makes continuous improvements to reduce variability and improve efficiency.

The vast majority of manufacturing process changes proposed by an innovator do not impact product structure or impurity profile. These simple changes – such as changes to equipment that do not have contact with the protein or changes to test methods – are easy to evaluate with purely analytical approaches, and no immunogenicity testing is necessary. However, when there are significant changes to the *biological* portion of the manufacturing process – that portion involving living organisms – a shift in the product profile is more likely. The innovator will make every effort to minimize the scope of these shifts, but some differences may remain: in these cases, immunogenicity testing may be necessary.

Indeed, experience with innovator biologics has been that significant changes to the biological portions of manufacturing processes have required non-clinical and clinical studies. Furthermore, on several occasions minor shifts in the product profile have had clinical effects that could not have been anticipated from purely biochemical evaluations of the molecule or by non-clinical (animal) studies.

By definition, the process used to manufacture a biosimilar will incorporate a biological portion that differs significantly from that of the innovator. A biosimilar manufacturer will have, among multiple other differences from the innovator, a different manufacturing site, different equipment, a different cell-line, different cell culture/fermentation conditions, different purification procedures, and a different formulation. As such, any biosimilar manufacturing process will include at its core a type of process change of such magnitude that, if introduced by an innovator, would lead to structural changes to the biologic, differences in the product's impurity profile and – inevitably – to a requirement for clinical studies and immunogenicity testing.

Implications for Naming

Before considering the naming of biologics and the implications of batch-to-batch variability or manufacturing changes, it is important to note the purpose of non-proprietary names:

> "The existence of an international nomenclature for pharmaceutical substances, in the form of INN [International Non-Proprietary Name], is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide."[12]

The question of naming biologics, therefore, relates to whether healthcare professionals, patients, and drug safety authorities are able to distinguish between "similar" biologic medicines that are made by different manufacturers. This is important to ensure robust pharmacovigilance and to prevent inappropriate switching of medicines. Accordingly, the nature of any variability, from a batch-to-batch basis or as a consequence of a manufacturing change, whether that be for an innovator biologic or a biosimilar, is not relevant to the practice of naming biologics.

Implications for Interchangeability

The generics industry asserts that the U.S. Food and Drug Administration (FDA) can make a decision on interchangeability for biologics, because, in effect, they make these decisions when they approve a manufacturing process change for an innovator biologic. This argument ignores the fundamental difference between making a change in a product whose safety and efficacy profile is known from extensive patient experience, and introducing a new biologic with limited patient experience.

With biosimilars in the marketplace, not only could a patient change biologic multiple times, but because there may be more than one biosimilar approved in each class, they could change multiple times between multiple products without the treating physician being aware. This could present a number of problems. For example, if a patient has an adverse reaction, it will be difficult to know which product caused the adverse response.

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?***

Human clinical studies should be mandated by statute for all biosimilars. The U.S. Food and Drug Administration (FDA) should be given discretion, however, to determine the nature and extent of the clinical studies that are required, as this will vary between different product classes (*e.g.* insulins, human growth hormones).

In terms of market acceptance, not requiring clinical studies would almost certainly have direct implications on whether healthcare professionals or patients would be prepared to use a biosimilar. The experience in Europe is proving that biosimilars that have been designed to be

[12] World Health Organization, "Guidance on International Nonproprietary Names," available at http://www.who.int/medicines/services/inn/innquidance/en/index.html (last visited April 17, 2008).

similar to an innovator biologic can have different clinical characteristics. Of the nine biosimilars to complete the European Medicines Agency (EMEA) review process, more than half (five) have demonstrated clinically unacceptable differences from the innovator in safety, efficacy or immunogenicity.[13]

A biosimilar will be manufactured using a process that is different from that of the innovator biologic, and this will inevitably lead to differences in the structures of the biosimilar and the innovator product. This expectation of differences has already been recognized by the EMEA in its guidelines for biosimilars and by the World Health Organization in its draft guideline on subsequent entry biological medicinal products:

> "It is not expected that the quality attributes in the similar biological and reference medicinal products will be identical."[14]

> "The structure of biotherapeutic is also very sensitive to various production parameters so that it is highly unlikely that one manufacturer can reproduce in fine detail, the biotherapeutic manufactured by another company."[15]

As it is not possible to predict the clinical consequences of such differences, it is necessary to conduct clinical studies in order to demonstrate similarity to the innovator biologic and an absence of clinically meaningful difference.

This has proven to be the case in Europe, where clinical data are necessary to reach decisions to approve or to reject biosimilar marketing applications. To date, nine separate biologics have completed the EMEA review process. Four of these (two growth hormones and two erythropoietins) have been approved,[16] one (interferon alfa-2a) has been rejected,[17] and three (soluble insulin, isophane insulin and biphasic insulin) were withdrawn by the applicant[18] prior

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[13] See European Medicines Agency, "European Public Assessment Report for Omnitrope, Scientific Discussion" (April 12, 2006); "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007); "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008); "Withdrawal Assessment Report for Insulin Human Long Marvel (International Nonproprietary Name: Isophane Insulin Injection)," Procedure No. EMEA/H/C/000846 (published March 19, 2008) (last visited May 1, 2008); "Withdrawal Assessment Report for Insulin Human 30/70 Mix Marvel (International Nonproprietary Name: Biphasic Insulin Injection)," Procedure No. EMEA/H/C/000847 (published March 19, 2008).

[14] European Medicines Agency, "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues," EMEA/CHMP/BWP/49348/2005 (Feb. 22, 2006), at p. 5.

[15] "WHO Guideline on Licensing Approaches for Subsequent Entry Biological Medicinal Products (DRAFT)" (April 15, 2008), at p. 3.

[16] See European Medicines Agency, "European Public Assessment Report for Omnitrope" (April 12, 2006); "European Public Assessment Report for Valtropin" (April 24, 2006); "European Public Assessment Report for Retacrit" (Dec. 18, 2007); "European Public Assessment Report for Binocrit" (Aug. 28, 2007)).

[17] See European Medicines Agency, "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007).

[18] See European Medicines Agency, "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008); "Withdrawal Assessment Report for Insulin Human Long Marvel (International Nonproprietary Name: Isophane Insulin Injection)," Procedure No. EMEA/H/C/000846 (published March 19, 2008); "Withdrawal Assessment Report for Insulin Human 30/70 Mix Marvel (International Nonproprietary Name: Biphasic Insulin Injection)," Procedure No. EMEA/H/C/000847 (published March 19, 2008).

to rejection. Another product (granulocyte-colony stimulating factor) has been granted a positive opinion by the EMEA,[19] but formal approval by the European Commission is pending.

In each of these cases, clinical data were necessary in order to support the decision reached by the EMEA, because a conclusion could not be reached based on the biophysical data alone. According to the EMEA, the approved biosimilars have demonstrated that, while there were biophysical differences between the biosimilar and the innovator, those differences were found to have no significant clinical consequences as proven by the clinical studies.

However, for the four biosimilars that were rejected or their applications withdrawn, clinical studies demonstrated that their safety and efficacy were not similar to the innovator – that is, there were clinically meaningful differences that were not predicted by the analytical or animal studies:

- In the case of the rejected interferon alfa-2a, which is used to treat hepatitis C, patients receiving the biosimilar were between 2 and 3 times more likely to have the disease return after an initial response.[20] Furthermore, the patients receiving the candidate biosimilar interferon were more likely to experience an adverse event.[21]

- In the case of the withdrawn insulins, which are used to control blood sugar levels in patients with diabetes, it was demonstrated that all three of the candidate biosimilars could not control diabetes in a similar way as the innovator insulins. One of the three insulins could potentially induce a blood sugar lowering effect 45% higher than the innovator insulin,[22] which is clearly not clinically acceptable nor, indeed, similar to the innovator. In addition, patients with type I diabetes who received the candidate biosimilar insulins were twice as likely to experience an adverse event.[23]

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?

For historical reasons, a small number of protein products have been approved under section 505 of the Federal Food, Drug, & Cosmetic Act. Pioneer protein products approved under this

[19] See European Medicines Agency, Committee for Medicinal Products for Human Use, "Summary of Positive Opinion for Tevagrastim (International Non-proprietary Name (INN): filgrastim)," EMEA/CHMP/67459/2008 (Feb. 21, 2008), at p. 1 ("Summaries of positive opinion are published without prejudice to the Commission Decision, which will normally be issued within 67 days from adoption of the Opinion.").
[20] European Medicines Agency, "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007), at pp. 20-22.
[21] European Medicines Agency, "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007), at p. 28.
[22] European Medicines Agency, "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008), at p. 16.
[23] European Medicines Agency, "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008), at p. 19; "Withdrawal Assessment Report for Insulin Human Long Marvel (International Nonproprietary Name: Isophane Insulin Injection)," Procedure No. EMEA/H/C/000846 (published March 19, 2008), at p. 19; "Withdrawal Assessment Report for Insulin Human 30/70 Mix Marvel (International Nonproprietary Name: Biphasic Insulin Injection)," Procedure No. EMEA/H/C/000847 (published March 19, 2008), at p. 19.

section are required to meet statutory standards of safety and substantial evidence of efficacy, which generally require two adequate and well-controlled clinical studies, or one adequate and well-controlled study plus confirmatory evidence. The very few protein products that have been approved under section 505(b)(2) based on reference to an approved product have generally required clinical trials to support their approval. For example, the FDA required clinical trials for the approval of Omnitrope® (somatropin recombinant), a biosimilar human growth hormone – which are relatively simple protein products that have been on the market for several decades.

Human clinical studies should be mandated by statute for all biosimilars. A biosimilar will be manufactured using a process that is different from that of the innovator product and this will inevitably lead to differences in the structures of the biosimilar and the innovator. This expectation of differences has already been recognized by the European Medicines Agency in its guidelines for biosimilars and by the World Health Organization in its draft guideline on subsequent entry biological medicinal products:

> "It is not expected that the quality attributes in the similar biological and reference medicinal products will be identical."[24]
>
> "The structure of biotherapeutic is also very sensitive to various production parameters so that it is highly unlikely that one manufacturer can reproduce in fine detail, the biotherapeutic manufactured by another company."[25]

As it is not possible to predict the clinical consequences of such differences, it is necessary to conduct clinical studies in order to demonstrate similarity to the innovator biologic and an absence of clinically meaningful difference.

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?

At this point in time it is premature to make a judgment about the post-market safety and efficacy of Omnitrope®(somatropin recombinant); however, in pre-market testing, patients in clinical studies of Omnitrope® did experience problems.

In the studies supporting approval of Omnitrope® in both the United States and Europe (and Australia) patients (children with growth deficiency) did experience a significant immunogenicity problem during clinical development, *i.e.*, before the approval of Omnitrope®. During the conduct of the phase III study that was necessary to understand if the efficacy, safety and immunogenicity of Omnitrope® was similar to that of the innovator biologic (Genotropin®), 57% of the children treated with Omnitrope® developed an immune reaction (as opposed to 2% of the patients who received the innovator biologic).[26] This immune response was not predicted

[24] European Medicines Agency, "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues," EMEA/CHMP/BWP/49348/2005 (Feb. 22, 2006), at p. 5.
[25] "WHO Guideline on Licensing Approaches for Subsequent Entry Biological Medicinal Products (DRAFT)" (April 15, 2008), at p. 3.
[26] European Medicines Agency, "European Public Assessment Report for Omnitrope, Scientific Discussion" (April 12, 2006), at p. 24.

by analytical testing. Omnitrope®'s sponsor addressed this problem by re-developing its purification process and conducting a second clinical trial to gain approval.

It must be stressed that this immunogenicity issue was resolved before Omnitrope® was approved in any region. However, if this product had been approved without clinical data, an unknown number of children in clinical practice – rather than "just" those children in a clinical trial – would have experienced antibodies to Omnitrope®. This experience illustrates the necessity of requiring clinical trials prior to approval of biosimilars to ensure patient safety.

b. Have patients been switched to Omnitrope from other recombinant human growth hormone products?

Since Amgen is not the sponsor of Omnitrope®, our response is limited based on information to which we have access. Based on sales data reported by IMS and other publicly available information, Omnitrope®'s uptake in Australia (product launched in November 2005), the European Union (product authorized for marketing in April 2006), and the United States (product launched in March 2007) has been minimal. For example, a report of January 2008 sales data in the United States showed that Omnitrope® had no more than a 1.5% market share of prescription renewals (TRx).[27] Griffiths McBurney cites discounting levels for Omnitrope® of 20% to 25% in Germany and 10% to 20% in the Australian human growth hormone market.[28] This is consistent with a report from Wachovia Capital Markets (10-20% discount).[29]

Patients, physicians, and payers may have not embraced Omnitrope® for a number of reasons, such as delivery method. Most brands of human growth hormone (except Tev-Tropin®) use an auto-injector, injection pen, or needle-free device to help minimize injection anxiety and difficulties. In the United States, Sandoz launched Omnitrope® as a lyophilized (freeze-dried) powder which must be reconstituted, drawn up into a syringe, and then injected into the child. HSBC Global Research hypothesized that the growth hormone market would be "highly resistant to 'basic' products such as Omnitrope®, where parents attempt to limit the impact of therapy on children as much as possible."[30] And Griffiths McBurney found that "[t]hrough our research, we believe that the limiting factor to the uptake of biogeneric growth factor products is not price. Instead, we believe that the slow uptake of such products is related to other dimensions, such as the product's delivery system and dosing convenience."[31]

[27] Sinclair A. and K. Scotcher, "Novo Nordisk: Initiating coverage with underweight and TP of DKK305," HSBC Global Research (March 27, 2008).
[28] Ordonez, C. & T. Connolly, "Accretropin Receives FDA Approval," Griffiths McBurney (Jan. 25, 2008).
[29] Farmer, G. et al., "Biogen Idec, Inc. BIIB: Shares unjustifiably rich on acquisition speculation," Wachovia Capital Markets LLC (Oct 10, 2007).
[30] Sinclair, A. and K. Scotcher, "Novo Nordisk: Initiating coverage with underweight and TP of DKK305," HSBC Global Research (March 27, 2008).
[31] Ordonez, C. & T. Connolly, "Accretropin Receives FDA Approval," Griffiths McBurney (Jan. 25, 2008).

In January 2008 Sandoz received FDA approval for a liquid formulation of Omnitrope® in a more convenient injection pen.[32] It remains to be seen whether there will be any significant market uptake for this new dosage form.

c. If the answer to part b is yes, how are payers handling the availability of this comparable product?

As discussed in part (b) of this question, thus far parents and physicians have not recognized Omnitrope® as having substantially greater incremental value over existing therapies.[33]

[32] See U.S. Food and Drug Administration, Approval History for Omnitrope, available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (last visited May 2, 2008).

[33] See, e.g., Sinclair A & K. Scotcher, "Novo Nordisk: Initiating coverage with underweight and TP of DKK305," HSBC Global Research, (March 27, 2008).

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?***

Yes, any biosimilar regulatory approval process should ultimately apply to biologics approved under the Federal Food, Drug, and Cosmetic Act (FFDCA) as well as those approved under the Public Health Service Act (PHSA).

The vast majority of therapeutic protein products are licensed under the Public Health Service Act (PHSA) as biological products. For historical reasons, however, a small number of therapeutic proteins that meet the definition of biological products have been approved under the FFDCA. In recent years, FDA has asserted that it has the legal authority to allow applications for follow-on protein products to be approved under section 505(b)(2) through a process that relies on the earlier approval of the innovator product,[34] a position that has not been without scientific and legal controversy.[35] Nonetheless, a very few small therapeutic protein products, such as Omnitrope® (somatropin recombinant) – have been approved under section 505(b)(2).[36] When Omnitrope® was approved, FDA stressed that the circumstances of that approval were unique and that it did not "mean that more complex and/or less well understood proteins approved as drugs under the FFDCA could be approved as follow-on products."[37]

Importantly, given the state of the science at the time of its enactment and the fact that biological products are licensed under the PHSA, section 505(b)(2) was not drafted with an eye towards the unique scientific, legal, and regulatory challenges presented by biosimilars. Indeed, not until 1999 did FDA suggest in a Draft Guidance that applications for drugs containing "naturally derived or recombinant active ingredients" could be accepted under section 505(b)(2).[38] Even then, there has been little articulation of the standards that would be required, leaving interested stakeholders to piece together information from individual approvals. In contrast, establishing a single statutory pathway for approval of all biosimilars under a new section of the PHSA would engender a much more coherent approach. It would allow Congress to address the unique issues associated with the approval and regulation of biosimilars and would create consistency and predictability for review of these products, instead of the case-by-case approach taken under FFDCA section 505(b)(2). We further believe that Congress can fashion a reasonable approach

[34] See, e.g., U.S. Food & Drug Administration, "Omnitrope (somatropin [rDNA origin]) Questions and Answers" (May 30, 2006), available at http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm (last visited April 28, 2008).
[35] See U.S. Food & Drug Administration, Dockets Nos. 2001P-0323, 2002P-0447, and 2003P-0408. See, e.g. U.S. Food & Drug Administration, Dockets Nos. 2004P-0231, 2003P-0176, and 2004P-0171.
[36] See U.S. Food & Drug Administration, "Omnitrope (somatropin [rDNA origin]) Questions and Answers" (May 30, 2006), available at http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm (last visited April 28, 2008).
[37] U.S. Food & Drug Administration, "Omnitrope (somatropin [rDNA origin]) Questions and Answers" (May 30, 2006), available at http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm (last visited April 28, 2008).
[38] U.S. Food & Drug Administration, "Draft Guidance for Industry: Applications Covered by Section 505(b)(2)" (Oct. 1999), at p. 5.

to transitioning biosimilar versions of FFDCA products into such a single approval pathway, as some introduced bills have done.

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?***

It is important to correctly understand the difference between a biosimilar product and a manufacturing process change introduced by an innovator with respect to an approved biologic. FDA and other regulatory agencies around the world have recognized that they differ to such an extent that it is inappropriate to directly apply any current legislation or regulatory practice that controls manufacturing process changes, to the legislative and regulatory standards that will be necessary for the approval of biosimilars.

The vast majority of manufacturing process changes proposed by an innovator do not impact product structure or impurity profile. These simple changes – such as changes to equipment that do not have contact with the protein or changes to test methods – are easy to evaluate with purely analytical approaches, and no immunogenicity testing is necessary. However, when there are significant changes to the *biological* portion of the manufacturing process – that portion involving living organisms – a shift in the product profile is more likely. The innovator will make every effort to minimize the scope of these shifts, but some differences may remain: in these cases, immunogenicity testing may be necessary.

Indeed, experience with innovator biologics has been that significant changes to the biological portions of manufacturing processes have required non-clinical and clinical studies. Furthermore, on several occasions minor shifts in the product profile have had clinical effects that could not have been anticipated from purely biochemical evaluations of the molecule or by non-clinical (animal) studies.

Accordingly, FDA has appropriately applied and communicated its discretion to decide whether a change in an approved biologic requires assessment through a clinical trial.

Through judicious application of this statutory discretion, expert knowledge and experience with biologics, and detailed discussions with innovator biologic manufacturers, patient safety has been and continues to be ensured. However, it is not scientifically appropriate to apply the experience with FDA's exercise of its statutory discretion with respect to process changes, to biosimilars.

By definition, the process used to manufacture a biosimilar will incorporate a biological portion that differs significantly from that of the innovator. A biosimilar manufacturer will have, among multiple other differences from the innovator, a different manufacturing site, different equipment, a different cell-line, different cell culture/fermentation conditions, different purification procedures, and a different formulation. As such, any biosimilar manufacturing process will include at its core a type of process change of such magnitude that, if introduced by an innovator, would lead to structural changes to the biologic, differences in the product's impurity profile and – inevitably – to a requirement for clinical studies and immunogenicity testing.

For these reasons, it would be scientifically inappropriate to apply historical experience of FDA decisions regarding manufacturing process changes to the creation of a legal pathway for approval of biosimilars. Structural differences between a biosimilar and the innovator are expected. The immune system is exquisitely sensitive and unpredictable in its ability to react to such differences – including differences that may not be detectable using state-of-the-art analytical techniques. As has been required in Europe and recommended by the World Health Organization, clinical testing, including testing for immunogenicity, of biosimilars must always be undertaken before approval.[39]

3. What FDA office should review FOBs?

As a general matter, applications for FDA approval of biosimilars will contain considerable data on various requirements, including detailed manufacturing information and pre-clinical and clinical data. Thus, it is essential that the reviewers responsible for these applications should likewise have the required expertise across the necessary disciplines, including biologic and biotechnology manufacture, protein purification, protein characterization, protein formulation, immunology and immunology testing standards, among others. To ensure robust, scientific, and reliable review of these applications, the review division within FDA that reviewed the innovator biologic should be assigned responsibility for the biosimilar.

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?

The use of any term in a statute that describes the similarity of a biosimilar to the innovator biologic needs to be qualified in terms of what characteristic of the biologic is being defined.

From the overall perspective, considering both the structural and clinical characteristics of a biosimilar, using the terms "highly similar" or "as similar as scientifically possible" are somewhat ambiguous, as the term "similar" is subjective. Using such ambiguous terms in a statute without an adequate definition would be problematic.

A better approach would be to describe the expectation that any biosimilar approved for marketing in the United States will have a similar safety, efficacy and immunogenic potential as the innovator in each approved indication, and the consequences for failing to meet such expectation. This being the case, a standard for ensuring sufficient similarity between the innovator biologic and the biosimilar would be an absence of clinically meaningful difference between the innovator biologic and the biosimilar.

[39] See European Medicines Agency, "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues," EMEA/CHMP/BWP/49348/2005 (Feb. 22, 2006), at p. 7, available at http://www.who.int/medicines/services/inn/innquidance/en/index.html (last visited April 17, 2008) and WHO Guideline on Licensing Approaches for Subsequent Entry Biological Medicinal Products (DRAFT)" at p. 36 (April 15, 2008).

In addition, the requirement that the biosimilar be "highly similar" must also take into account structural similarity. In the context of well-characterized biologics (which at present means recombinant proteins with well-defined sequence and structure) this should include structural characteristics like an identical amino acid sequence, identical intramolecular bonding pattern, and post-translational modifications such as carbohydrate structures that largely overlap in nature and prevalence with those structures observed in the innovator biologic.

Therefore, the statute should require a biosimilar applicant to demonstrate an absence of clinically meaningful difference between the innovator biologic and the biosimilar through the conduct of clinical studies. The FDA then has the knowledge and expertise to meet this statutory expectation.

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?***

The issue of biosimilars raises very complex scientific and regulatory issues that should be addressed in regulations or guidance. Scientific experts and other interested stakeholders should therefore have an opportunity to comment on the development of appropriate approval standards. As the U.S. Food and Drug Administration (FDA) has acknowledged, it should have the most current and most relevant scientific information available to it before setting any regulatory standards by which biosimilar applications will be considered. By defining these standards for approval in formal guidance documents after seeking public comment from experts in the area, FDA will not only provide consistent standards for biosimilar manufacturers to meet, the agency will also generate confidence in the biosimilar approval process among healthcare providers and patients, and meet the legitimate expectation that the agency will first define the relevant standards and then assess applications in light of such standards. Moreover, the European approach provides a good model for – and reflects the important advantages of – engaging in a public and transparent guidance development process.

By promoting the development of guidance and doing so in a public and transparent manner, FDA will be able to receive valuable input from healthcare providers and patients – who are the ultimate end-users of innovator biologics and who have the most real-world, clinical experience in their use. By ensuring that healthcare providers and patients have a meaningful opportunity to contribute to the development of biosimilar approval standards, FDA will be instilling greater confidence in the stakeholders who have the greatest interest in ensuring the safety of biosimilars in the United States – patients and their physicians These groups will be familiar with, and have confidence in, the standards for approval which a newly-approved biosimilar would be required to meet, if they themselves were involved in the very development of those standards.

By defining product class-specific guidances (*e.g.* for erythropoietins, insulins, growth hormones, etc.) physicians and patients will know that *any* newly-approved biosimilar in the relevant class will have met a certain, defined standard criteria for approval.

Without such a defined standard in the form of a product class-specific guideline, biosimilar applicants would negotiate their own individual approval standards with FDA, involving different clinical data sets and acceptance criteria. Such a case-by-case approach would not only create inconsistency in approval standards, but it would increase the need for physicians and patients to review each newly-approved biosimilar on its own merits – as each approved biosimilar could be more or less "similar" to the innovator biologic, supported by different data in different patient populations.

The European Union's biosimilar legislation required the issuance of detailed guidelines describing the data necessary to support marketing authorizations for biosimilar products.[40] European authorities have since formally adopted guidelines, which were drafted with substantial public and industry input. Specifically, the European Medicines Agency (EMEA) issued concept papers (with a period for the public to submit comments), then draft guidelines (with a period for the public to submit comments), and then separate product-specific guidelines (with a period for the public to submit comments). The final guidelines entered into effect approximately six months after their final adoption. All of the EU biosimilar guidelines were developed using a transparent and public process, involving consultations of all stakeholders. The EMEA has also published an overview of all comments on the guidelines and explained the rationale behind the EMEA's acceptance or non-acceptance of the points made in consultation.

Contrary to criticism that adopting such a guidance development process in the U.S. would take too long, the European experience shows otherwise: guideline development from start to finish took less than two years. The stakeholders in the United States deserve no less of a robust, transparent process for development of approval standards for biosimilars.

The FDA has recognized the importance of the scientific input that comes from a public process. As Dr. Janet Woodcock, then serving as FDA's Chief Medical Officer has stated before the Energy and Commerce Committee of the U.S. House of Representatives, "[I]t is very important in this area, follow-ons, that we stay up to date with the science and therefore we have a dynamic public process that keeps giving us the scientific input that we need."[41]

It is essential that FDA undertakes a thoughtful, deliberate, and transparent assessment of the scientific and regulatory standards for approval of biosimilar products and that the agency solicits input from the public before developing regulations and product class-specific guidances. Requiring the development of guidances detailing the approval standards will not only promote consistency in biosimilars, it will also increase the medical community's and patients' confidence in approved biosimilar medicines.

[40] See Annex I to Directive 2001/83/EC.

[41] Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration, before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007).

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

This question is perhaps most appropriately directed toward the U.S. Food and Drug Administration (FDA), which is the most capable party to make these types of determinations about the resources that it would need for review of biosimilars. We would note, though, that we strongly support FDA having whatever resources are necessary to review biosimilar applications in a timely manner without compromising review quality. Indeed, the current Administration's FY 2009 budget proposal authorizes user fees to fund a biosimilars review program.[42]

Although the precise data package requirements for a biosimilar will likely vary according to product class, indications sought, and a number of other criteria to be determined by FDA, the approval of a biosimilar product nevertheless will likely require a robust review of quality, pre-clinical and clinical data. The application of user fees to the biosimilar review process will help to ensure that FDA is able to complete that review and take appropriate action while continuing to preserve its high standards for drug product safety, effectiveness, and quality.

In addition to helping to ensure adequate funding of FDA's review of applications, user fees will also help FDA to monitor biosimilars after they are approved and introduced into the market – and, importantly, to take appropriate action with respect to post-market safety. Congress has increased user fees over the years to provide FDA with the resources necessary to exercise its post-approval authorities. The application of user fees to biosimilars is consistent with FDA's mission to protect patient safety by conducting rigorous post-market surveillance and exercising its post-market authorities to ensure and enhance the continued safety and effectiveness of a marketed drug or biologic.

[42] See "President's Request Would Give U.S. FDA $2.4 Billion in Fiscal 2009," International Pharmaceutical Regulatory Monitor, Vol. 36, No. 2 (Feb. 15, 2008).

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?***

Before addressing this series of questions on substitution, it is important to understand what this term means. There are essentially two possible meanings:

- A decision that is made by the treating physician to prescribe a different drug than had been previously prescribed. The physician has access to all the necessary information about the patient, the disease and the medicines; accordingly, he or she is able to make a fully informed decision about which medicine(s) should be used to treat a patient.

- A decision that is made by the dispensing pharmacist to dispense a generic version of the drug that was prescribed.

The first definition, in which the physician is making the decision, is currently permitted for all FDA-approved medicines (both biologics and small-molecule drugs).

For the purposes of these responses, we will consider substitution as it is defined above in the second bullet, where the dispensing pharmacist, not the treating physician, makes the decision. Although governed by state pharmacy practice acts, which naturally differ, the general scientific underpinning for these types of determinations is that the FDA has determined the two products (the innovative drug and the generic) to be "therapeutically equivalent."[43] In order to be considered "therapeutically equivalent," the two drugs must have, among other things, identical amounts of the same active ingredient and be bioequivalent.[44] The agency believes that "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."[45]

The challenge in assessing substitution in the context of biologics is how to establish that two (or more) biologics that are similar – but not identical – to each other, can be substituted repeatedly for one another with no clinical consequences. This is no simple undertaking, as there is no precedent for a prospectively-designed clinical study or test that would address this question.

One must also consider the practical issues related to establishing substitution of biologics, such as the impact on post-market safety surveillance (pharmacovigilance). It is essential that when new medicines are approved, we can accurately monitor them in the marketplace. This enables FDA and/or the manufacturers concerned to rapidly and accurately take appropriate action if and

[43] See, generally, U.S. Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 28th Edition, at pp. iv-v (discussing background of the publication as providing "public information and advice to state health agencies, prescribers, and pharmacists"). This publication is commonly referred to as "the Orange Book."
[44] Id. at p. vi.
[45] Id. at p. vii.

when safety concerns with a product arise. If substitution were permitted for biologics, a patient could receive multiple biologic products over a period of time without the physician being aware that this was taking place. This could lead to inaccurate reporting of adverse events and an inability to determine exactly which products a patient has received. It is essential that all biologics (innovator or biosimilar) are subject to effective post-market surveillance to fully assess the safety of these products. Any practice that hinders the ability to accurately report post-market safety data should therefore be avoided.

In considering this pharmacovigilance challenge, it is instructive to examine the substitution decisions being reached in Europe. Evidence from Europe is that the practice of substitution by the pharmacist without the prior informed consent of the treating physician is rejected in all EU member states that have taken a position on this matter (including France, Germany, the United Kingdom, Italy and Spain[46]). It is unlikely that the remaining member states that have yet to reach a decision on this matter will allow or encourage the practice of substitution for biologics. The European Medicines Agency has stated that "[s]ince biosimilars and biological reference products are not identical, the decision to treat a patient with a reference product or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."[47] The French regulatory agency published its views in a recent article in the scientific journal *Hormone Research* regarding growth hormone; its comments with regard to substitution and pharmacovigilance are quoted in full below:

> "Substitution:
>
> Biosimilar [biological medicinal products] BMPs are authorized throughout Europe through the EMEA-centralized procedure. The subsequent possibility of substitution is the responsibility of the individual member state.
>
> In this context it is important to remember that biosimilar BMPs are not generic medicinal products. Detected or undetected differences between the biosimilar and the reference BMP may cause differences in safety or the efficacy profile. Considering that these differences may not be observed until more experience with these biosimilar BMPs is acquired, a systematic and uncontrolled substitution, based on the prescription of the international common denomination of the active substance, does not appear reasonable at this time. In addition, biosimilar BMPs remain, in the first place, biological medicinal products with their own quality profile, related to their own manufacturing process. In principle it is not recommended to switch patients from one BMP to another. There is no reason to depart from this recommendation for a biosimilar product.

[46] See, for example, "Order No. SCO/2874/2007 of 28 September 2007 determining which medicaments constitute an exception to possible substitution by a pharmacist in accordance with Section 86.4 of Law No. 29/2006 of 26 July 2006 on guarantees and the rational use of medicaments and health products," in Boletín Oficial del Estado, No. 239 (Oct. 5, 2007), at pp. 40495-40496.

[47] European Medicines Agency, "Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products)," EMEA/74562/2006 (June 22, 2007) at p. 1.

> Moreover, clinical efficacy and safety of biosimilar somatropins has only been shown in one, albeit sensitive, population of patients. The extrapolation to other, less sensitive populations still needs to be proven in practice. In addition, the duration of trials was limited and possible changes in efficacy and safety in long-term use cannot be excluded. A widespread substitution would prevent detecting these potential changes.
>
> Data on currently approved BMPs suggest that an important amount of clinical experience is necessary to obtain a thorough knowledge of the long-term safety and efficacy of these products. Therefore physicians should be involved in decisions to substitute any BMP. In this respect it is also essential to have excellent records of the treatments received in patients' clinical files, allowing physicians to trace closely the products used in case of occurrence of an adverse event."[48]

In conclusion, science may evolve to the extent that the risks associated with allowing substitution of biologics could be somehow evaluated. However, permitting any systematic and uncontrolled substitution by pharmacists would significantly impair the ability of pharmacovigilance systems to accurately identify the root cause of any future safety or efficacy issues with that class of biologic.

It therefore seems prudent to ensure that the treating physician is always involved in advance in the decision to change a biologic (whether innovator or biosimilar).

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

Clinical studies that address the question of the clinical consequences of repeated changes of biologic have never before been designed or conducted. Furthermore, they would raise significant ethical questions. The studies would have to be designed to ensure that repeated changes in biologic do not induce an adverse event. As such, they could actually induce adverse events in patients, and there would likely be significant questions raised by the U.S. Food & Drug Administration (FDA), IRBs (institutional review boards, or ethics committees), healthcare professionals, and patients. As such, while such studies could in theory at least be designed, there would be very real ethical issues involved in actually conducting them.

Even if such studies could be designed/conducted in a way that could overcome these significant ethical and methodological concerns, they would be intended to create a circumstance in clinical practice that would significantly impair the ability of pharmacovigilance systems to accurately identify the root cause of any future safety or efficacy issues with that class of biologic.

[48] M. Pavlovic, et al., "Similar Biological Medicinal Products Containing Recombinant Human Growth Hormone: European Regulation," Hormone Research, Vol. 69, No. 1, pp. 14-21 (2008).

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.***

Any mechanism that seeks to address the clinical consequences of systematic and uncontrolled substitution by pharmacists (substitution) would be designed to create a circumstance in clinical practice that would significantly impair the ability of pharmacovigilance systems to accurately identify the root cause of any future safety or efficacy issues with that class of biologic.

We do not believe that creating such a circumstance in clinical practice is wise; therefore, any statute addressing this issue should ensure that the treating physician is always involved in advance in the decision to change a biologic (whether innovator or biosimilar).

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?***

Any mechanism that seeks to address the clinical consequences of systematic and uncontrolled substitution by pharmacists (substitution) would be designed to create a circumstance in clinical practice that would significantly impair the ability of pharmacovigilance systems to accurately identify the root cause of any future safety or efficacy issues with that class of biologic.

We do not believe that creating such a circumstance in clinical practice is wise; therefore, any statute addressing this issue should ensure that the treating physician is always involved in advance in the decision to change a biologic (whether innovator or biosimilar).

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?***

There are several potential risks to the patient if systematic and uncontrolled substitution of biologics by pharmacists is permitted in clinical practice.

We simply do not know what will happen when patients repeatedly change from one biologic to another. Since there may be clinical implications to such repeated and uncontrolled changes, it would be clinically prudent to not permit such changes until we have evidence to show that substitution of biologics does not pose a risk to public health.

One such concern, as described by Dr. Janet Woodcock, is that repeated, uncontrolled changes between similar biologics might induce an immune response.[49] Such a circumstance has indeed

[49] Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration, before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007 ("For many follow-on protein products -- and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness.")

been seen and acted upon by the European Medicines Agency (EMEA) with recombinant factor VIII (rFVIII) products, which are used to treat patients with hemophilia by helping their blood to clot. In this case, observations have been made in medical practice whereby patients who change from one innovator rFVIII to another have been found to be more likely to develop immune-mediated inhibitors (*i.e.* antibodies). The EMEA is currently taking measures to collect more reliable data, improve pharmacovigilance, and introduce a statement in the product's labeling.

Biosimilars and innovator biologics may not be approved for exactly the same indications for use. Since the dispensing pharmacist does not necessarily know for which indication a patient has been prescribed a biologic, systematic and uncontrolled substitution of biologics may lead to patients being dispensed a biologic that is not approved by FDA for use in their disease. This is certainly the case for Omnitrope®, a product that has been approved for some – but not all – of the indications for which the innovator biologic (Genotropin®) has been approved.[50]

This is also proving to be the case in Europe, where the biosimilar epoetin alfas (EPOs) manufactured by Sandoz and Hospira are not approved for subcutaneous use (injection under the skin) in patients with anemia due to reduced kidney function or in pre-donation programs (Sandoz EPO) or prior to elective surgery (Hospira EPO). Neither EPO was approved for subcutaneous use (injection under the skin) in patients with anemia due to reduced kidney function, because the data submitted by both companies before approval did not adequately address the risks of patients developing an immune response. The EMEA has therefore required that Sandoz and Hospira conduct clinical studies to address this risk.[51]

Systematic and uncontrolled substitution of biologics by pharmacists could therefore lead to potentially serious safety issues if, for valid clinical reasons, the U.S. Food and Drug Administration does not approve certain indications.

Biosimilars will be approved based on different clinical data than the innovator biologic. This being the case, a physician may choose to prescribe a specific biologic (whether biosimilar or innovator) based on his or her own review of the clinical data and his or her own clinical judgment regarding which product is the best therapy for the patient. This decision should not be overturned by a pharmacist or health insurer, who clearly will not have the same detailed knowledge of the individual patient as the physician does.

We do not believe that creating such a circumstance in clinical practice is wise – therefore, any statutory language should be written to ensure that the treating physician is <u>always</u> involved, in advance, in the decision to change a biologic (whether innovator or biosimilar), both for patient

[50] See U.S. Food and Drug Administration, Label and Approval History for Omnitrope, available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory (last visited May 1, 2008); Label and Approval History for Genotropin, available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory (last visited May 1, 2008).

[51] See "European Public Assessment Report for Retacrit" (Dec. 18, 2007), available at http://www.emea.europa.eu/humandocs/Humans/EPAR/retacrit/retacrit.htm (last visited May 1, 2008); "European Public Assessment Report for Binocrit" (Aug. 28, 2007), available at http://www.emea.europa.eu/humandocs/Humans/EPAR/binocrit/binocrit.htm (last visited May 1, 2008).

safety reasons and to allow pharmacovigilance systems to accurately identify the root cause of any future safety or efficacy issues with that class of biologic.

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

The substitution of biosimilars will play a significant role in how they will compete in the marketplace. The current system of generic substitution that is encouraged by health plan formularies, prescriber perception, and state generic interchange laws, is predicated on the substitute product being identical to the reference product. In other words, it is the identicality of the generic drug and the brand drug that allows for competition in the marketplace. In contrast, if the biosimilar is deemed similar (not identical) to the innovator, the competition dynamic will be more akin to therapeutic alternative competition, or competition between two branded products. At present, the U.S. Food and Drug Administration does not expect to be able to deem most biosimilars as identical.[52]

[52] Woodcock, Janet et al., "The FDA's Assessment of Follow-on Protein Products: A Historical Perspective," Nature Reviews (April 2007), at p. 4. See also Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration before the Committee on Oversight and Government Reform, United States House of Representatives, "Follow-on Protein Products" (March 26, 2007), pp. 11-12, available at http://oversight.house.gov/documents/20070326104056-22106.pdf (last visited April 25, 2008).

Patents

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

The current effective patent term for pharmaceuticals varies widely. Under current law, a patent term is 20 years from the date that an inventor files the application for its patent with the U.S. Patent & Trademark Office. However, a patent application for a pharmaceutical must be filed very early in the drug development process, long before the medicine is ready for patients. A new drug may only be marketed after the product has been thoroughly tested in humans, the drug sponsor has submitted a New Drug Application (NDA) or Biologics License Application (BLA) with the FDA, and the FDA has reviewed and approved the application. During that lengthy period of time, a significant portion of the drug's patent term will have elapsed since the patent application was filed.[53] Thus, while the nominal patent life of a product lasts 20 years from the date of patent application, the effective patent life of a pharmaceutical is the time period between the date that the drug is approved by the FDA and the date when the last patent on the product expires.

Congress acknowledged that significant patent life is lost during a drug's clinical development and regulatory review periods, and in 1984 enacted the "Drug Price Competition & Patent Term Restoration Act", commonly referred to as the Hatch-Waxman Act, which provides for a patent term restoration period of up to five years of additional patent life for new drugs or biologics, with total effective patent life of up to 14 years.[54] Even with the patent term extension provided under Hatch-Waxman, however, the effective life of a pharmaceutical patent falls well short of the 20-year nominal patent term provided under current law.

The effective patent life varies widely. Economist Henry Grabowski investigated the new chemical entities (NCEs) that were first marketed between 1991 and 1995 and found that those products had an average effective patent life of 11.7 years, which included, on average, a Hatch-Waxman patent term extension of 2.3 years.[55] This calculation, however, considers products whose patents were issued under the previous patent term of 17 years from the date the patent was issued. The patent law changed in 1995 and applications filed after June 8th of that year receive 20 years from the date the patent application is filed, rather than 17 years from the date the patent is issued. The average effective patent life for products under the 20-years patent term may be different than Grabowski's calculation.

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[53] Typically, a pharmaceutical firm applies for a patent to cover a potential new drug candidate long before the company's Investigational New Drug application (IND) is approved by the FDA: the approval of the IND essentially gives the company permission to begin clinical studies of the product in human subjects. The clinical development process for a new drug then takes place, and if the clinical testing of the drug candidate is successful, the company files an NDA or BLA seeking FDA approval of the product. If and when FDA approves the company's NDA or BLA, and only then, may the company market the new drug to the public.

[54] See P.L. 98-417, "Drug Price Competition and Patent Term Restoration Act of 1984" (Sept. 24, 1984).

[55] Grabowski, Henry, "Patents and New Product Development in the Pharmaceuticals and Biotechnology Industries," in John Duca, ed., Science and Cents: The Economics of Biotechnology, Federal Reserve Bank of Dallas (2003), at p. 100.

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?***

While the concepts underlying the Hatch-Waxman Act may be useful tools in Congress' discussion on biosimilars, the experience of the pharmaceutical industry over the past twenty-four years has demonstrated that the complex and intricate statutory framework of the Act is not a good model to adopt for an abbreviated approval pathway for biosimilars. Hatch-Waxman appropriately recognized the need for data protection and a mechanism for resolving patent disputes, but the data protection provided by the Act is inadequate to encourage and reward innovation in biotechnology. Additionally, by granting 180 days of exclusivity to the first generic product, the Act provided a perverse incentive to challenge the innovator's patents early and often – usually only a few years after the innovator began selling its product and years before the patents expired. This pervasive litigation has become a huge distraction to the pharmaceutical industry and caused a good deal of unnecessary uncertainty as to the commercial opportunities for both the innovator and the generic companies.

Hatch-Waxman is not a good model for a biosimilar approval pathway for a number of additional reasons. First, the balancing of interests under Hatch-Waxman was based on the ease of generic applicants in showing structural identity of the generic product to the innovator's product. This structural identity suggested sameness in clinical safety and efficacy but also was nearly conclusive on the issue of patent infringement. The innovator had a patent on the structure of the compound, and thus, it was easy to show that the generic compound infringed the innovator's patent. In contrast, as discussed above, a biosimilar biological product will only be "similar" and not "identical" to the innovator's product. The biosimilar product will be made by different cell lines under different conditions than the innovator's product thus ensuring that the two products will be different to some degree. This product difference not only imposes a requirement for sufficient clinical testing to ensure the safety of the product (as discussed above), but it allows the biosimilar applicant to argue that the product is different from the innovator's product and thus does not infringe the innovator's patent. Under a Hatch-Waxman type of regulatory scheme for biosimilars, the innovator would not have access to sufficient information on the biosimilar (until well into discovery in litigation) to know how the biosimilar was made, the extent of product differences and whether these differences impact the issue of patent infringement or not.

Second, the nature of the patent rights for biologics is different than the patents that are obtained for small-molecule pharmaceuticals. For many biological products, the patent rights that protect the innovator's product are process patents. Hatch-Waxman does not allow listing of process patents, and the regulatory scheme provides no vehicle for disclosing process information on how the generic product was made to the innovator.

Third, Hatch-Waxman fails to sufficiently recognize and reward the separate and independent purposes of the patent system and the regulatory scheme of data protection and the separate investments required by the innovator to secure a patent and a clinical data set that demonstrates

the safety and efficacy of the product. Patents protect the initial invention – the molecule, or new way of making a product, and typically are issued very early in the research process, perhaps even before it can be known whether the molecule has any therapeutic or commercial potential. The patent term begins ticking away the minute the patent application is submitted to the U.S. Patent & Trademark Office (PTO) (or, for applications submitted before June 8, 1995, the date the patent is issued) – usually years before a drug company has received FDA approval to begin marketing a product. Once issued, a patent provides exclusive rights to what is claimed as the invention. A large majority of the 1400 biotech companies in the U.S. are small research companies that make inventions, file patent applications and then look to license the commercial rights to its products to other companies.

The purpose of data exclusivity, on the other hand, is to encourage companies to embark on the lengthy, complicated, and risky clinical development program required for FDA approval. The average cost of developing a biologic product through FDA approval has been estimated to be about $1.2 billion.[56] If successful in obtaining that approval, data exclusivity allows an innovator a period of time after FDA approval during which a generic may not rely on the valuable data developed by the innovator to gain FDA approval. Without such a period, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved.

It is important to note that the protection conferred by data exclusivity is different from that provided by a patent. A patent would prevent another manufacturer from marketing the same drug (or pay damages for infringement), even with a full application supported by its own data. Data exclusivity simply prevents reliance on the innovator's data for FDA approval, but does not prohibit a manufacturer from gaining approval of a product based on their own data.

In summary, the Hatch-Waxman model has resulted in excessive patent challenges early in the product life that has added unnecessary expense to the health care system without benefiting patients, including those waiting for new cures. The generic drug companies are encouraged to challenge innovator patents early as a result of the way Congress designed the 180 day exclusivity period awarded to the first successful challenger, whether or not the challenge has merit. Similarly the so called "paragraph IV" certification process that was intended to filter out unwarranted and meritless patents has become little more than a perfunctory step in litigation.

Instead of duplicating this system, a biosimilar regime should include a simplified mechanism for facilitating resolution of patent disputes before a biosimilar product comes to market and a process for enforcing valid patents. Such a mechanism should ensure notification of the innovator of possible infringement, notification of the biosimilar manufacturer of patents that may be infringed, and an opportunity to bring an infringement suit early enough before the end of the data exclusivity period in order to ensure resolution before the biosimilar goes to market. This certainty benefits all parties by limiting unnecessary litigation and reducing the infringement risk faced by the biosimilar manufacturer.

[56] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008).

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?***

Under the current patent system, biotechnology patents do provide essential protection for biological products. However, many biotechnology patents are process related – that is, the patent either protects a product that is made by a particular claimed process or it protects the process itself which comprises a series of steps. For many biotech products, a typical way to characterize the product is by the process by which it was made. This is a distinct difference from the patents relating to traditional small-molecule drugs which usually recite a chemical structure for the active ingredient. The chemistry for producing small-molecule products is usually already known so process patents for those products are rare. This heavy reliance on process patent protection for biotechnology products is an important consideration in the discussion on biosimilars.

The Hatch-Waxman model requires a generic drug (an Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents. The assumption of patent infringement that is inherent in the generic drug model may not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness". Put simply, for scientific reasons it is *impossible* to make an identical copy of a biologic medicine. Biosimilar manufacturers can be expected to claim they have "designed around" the innovator patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections for innovators of biotechnology products.

Any pathway for abbreviated approval of biosimilars must consider both patents and data exclusivity. Patents protect the invention, i.e., the product or the process, but do not protect the intellectual property that is embodied in the preclinical and clinical data submitted to the FDA for product approval. This data is very expensive to obtain and has significant value separate and apart from the product itself and the patent rights. Data exclusivity protects the information gathered by the innovator to demonstrate the safety and effectiveness of the product and is intended to encourage companies to embark on the lengthy, complicated, and risky development program required for FDA approval. Without a significant period for data exclusivity, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved. The data exclusivity period runs concurrent with the patent term, beginning at the point the product is approved for marketing. Together, patents and data exclusivity provide a limited period of protection for the innovator to attempt to recover the cost of product discovery

and development. Without this opportunity, investment in biotechnology would be significantly diminished.

4. ***What procedures, if any, should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims by a biosimilar company and to ensure timely resolution of legal disputes?***

A robust patent system – including a process for enforcing valid patents – and adequate data exclusivity are necessary to encourage investment in biotechnology. To these ends, a biosimilar approval pathway should include a mechanism for facilitating resolution of patent disputes before a biosimilar product comes to market. This will help provide a level of certainty for investors in both innovative and biosimilar products and thus foster the development of both industries.

Identifying potential infringement is a necessary first step in facilitating patent dispute resolution. Requiring the FDA to publish a notice in the *Federal Register* when it accepts an application seeking approval of a biosimilar biologic would be an efficient and appropriate way to ensure that all interested parties have an opportunity to learn of potential patent infringement. Prompt public notice will enable anyone who may have an interest in a relevant patent to take action to protect their intellectual property rights. Such a procedure would impose only a minimal burden on the agency. Upon submission of its application to FDA, a biosimilar applicant should be required to promptly send its application, along with information about the proposed biosimilar product and about its manufacturing process, to the reference product sponsor and to any third party who requests the information in writing from the biosimilar applicant in order to further facilitate the resolution of patent disputes.

It is important that the litigation provisions for early patent resolution be designed in a way that encourages resolution of all questions of patent validity and infringement in a timely manner but avoids wasteful, costly and unnecessary disputes that simply function to harass responsible manufacturers on both sides of the process. A litigation scheme that effectively balances the interests of both the patent holder and the patent challenger will enjoin infringement after a patent is found to be valid and infringed.

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?***

Third party patent holders should have an opportunity to protect their intellectual property interests independent of the reference product sponsor's efforts to protect its intellectual property. Public notification by the FDA that it has received the biosimilar application and an opportunity for third-party patent holder to request a copy of the application and manufacturing information from the applicant will facilitate protecting the interests of all parties. Public notice will make early resolution of patent disputes possible and enable biosimilar manufacturers to avoid going to market at risk.

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?***

Identification of patents at issue can be achieved without the listing and notification provisions of Hatch-Waxman and without involvement of the FDA. Within a reasonable time after the biosimilar applicant provides a copy of its FDA application to the innovator, the innovator should be required to identify to the biosimilar applicant the patents which it believes would be infringed by the applicant's proposed biosimilar.

FDA's role in patent enforcement should be limited to requiring the agency to take appropriate measures to ensure transparency in its handling of biosimilar applications in order to avoid aiding in the theft of intellectual property. Requiring FDA to publish a notice in the *Federal Register* that the agency has received a biosimilar application would create only a minimal administrative burden and would be an inexpensive and effective means of providing notice sufficient to allow interested parties to protect their interests. In doing so, public notice would facilitate the resolution of patent disputes.

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?***

Reference product manufacturers must be given an adequate period of data exclusivity in the context of the establishment of a regulatory pathway for biosimilars. Importantly, the data exclusivity period is not in addition to the patent term, but runs concurrently with the patent from the time of FDA approval. A data exclusivity period of fourteen years is necessary to ensure ongoing biotech innovation.

Patents and data exclusivity both serve to encourage innovation but they protect different things. Patents protect the invention by allowing the inventor to prohibit others from using the discovery for a limited period of time. Without this protection, others could copy the invention and compete with the innovator. Data exclusivity is necessary in the context of an abbreviated FDA approval mechanism that permits an attempted copy to reference the data of the innovator demonstrating the safety and efficacy of a product rather than develop its own data.

Data exclusivity protects the data in the innovator's regulatory application by – for a limited period of time – prohibiting others from relying on the innovator's data to submit an application to FDA for marketing approval and prohibiting FDA from approving an application that relies on the data of others (including by referencing the fact of approval, rather than the specific data). Thus, data exclusivity protects the innovator from free riding by an attempted imitation, but only with regard to its data. Another product could be approved during this period using its own data, thus both patent protection and data exclusivity are necessary for both.

Data exclusivity is particularly important in the context of biosimilars. The Hatch-Waxman model requires a generic drug (an Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents. The assumption of patent infringement that is inherent in the generic drug model may not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness". Put simply, for scientific reasons it is *impossible* to make an identical copy of a biologic medicine. Biosimilar manufacturers can be expected to claim they have "designed around" the innovator patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections – namely data exclusivity – for innovators of biotechnology products.

It is important to note that <u>data</u> exclusivity is very different from <u>market</u> exclusivity. Market exclusivity would prevent any other manufacturer from obtaining approval of the same or a

similar drug (depending upon the specific statute), even with a full application supported by its own data.

As discussed above, both patents and data exclusivity are important means of encouraging investment in biotechnology, but they serve different roles. For the following reasons, a 14 year period of data exclusivity is justified in addition to patent term restoration:

- **The break-even point for a biologic is 12.9 to 16.2 years on the market.**[57] Currently, the cost to develop a new biological therapy is estimated at $1.2 billion, an increase of three times what it cost to develop a drug back in 1984.[58] In addition, the "break-even" point for biologics has been found to occur after it has been on the market somewhere between 12.9 and 16.2 years. Therefore a 14 year period of data exclusivity is appropriate to recognize this increased cost and to provide the proper incentives to invest in products which may fail at any stage in the research and development process.

- **New uses for existing therapies.** The most important use of a new medicine may not be apparent for years. Many biotechnology companies continue to research additional uses for their medicines. Indeed, many companies get original approval of their products for one indication and then discover new uses and indications for their therapies, sometimes in different diseases years later. An example of this is a biologic called Herceptin, developed by Genentech, which gained approval in the adjuvant cancer setting eight years after its original approval in the metastatic setting.[59] Without a substantial period of data exclusivity, the incentive to find new and novel uses for therapies will be significantly diminished.

- **The biotechnology industry is young and susceptible to disruption.** The biotechnology industry is very new compared to the pharmaceutical industry at the time a generic drug pathway was established. The biotechnology industry is less than 30 years old and few biotech companies have products on the market. Out of the more than 1400 biotechnology companies, only 20 of them are currently profitable. Small companies account for two-thirds of the industry's clinical pipeline and these companies rely on venture capital funding to finance their research and development. Without data exclusivity, the hope for a return on investment would be greatly diminished and therefore so would venture capital funding. The biotech industry is vulnerable to market instabilities and maintaining an incentive structure that promotes investment in uncertain

[57] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007).
[58] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008). Hatch-Waxman preserved 5 years of data exclusivity for innovative small molecule drugs to recoup the $397 million (adjusted to 2005 dollars) it cost then to develop a new drug.
[59] "The approval for Herceptin in the adjuvant setting occurred eight years after the original approval in the metastatic setting and involved more than 3,500 women in multiple randomized clinical trials. These trials can take easily more than five years from inception to completion, at huge cost, without any assurance of clinical success. Herceptin in the adjuvant setting reduced the risk of cancer recurrence by 50 percent, and if the cancer doesn't recur, these women cannot die from it." Testimony of Dr. David Schenkein, Vice President, Clinical Hematology/Oncology, Genentech, before the House Committee on Energy and Commerce, May 2, 2007.

research and development is essential to the future of this U.S. industry and finding cures for patients.

- **The potential cost in terms of human suffering as a result of inadequate incentives for biotech are huge.** Many devastating diseases lack effective treatments or cures. The impact on human lives and the national economy are enormous. If just one medicine is approved that can delay the onset or slow the progression of Alzheimer's disease by five years, Medicare and Medicaid could save $100B in annual costs by 2020.[60] In 2006, biopharmaceutical companies had 42 drug candidates for Alzheimer's in their pipelines.[61] Cancer is another example. The National Institutes of Health estimated that, in 2006, $78.2B was spent on total direct medical costs for cancer.[62] In 2004, the national cost burden for patients with metastatic bone disease (MBD) was estimated at $12.6B.[63] This means that, even if a cure is found for no other cancer except MBD, 17% of the total direct medical cost for cancer could be eliminated. There are currently fourteen industry-sponsored studies actively recruiting patients with metastatic bone disease.[64] Four of these trials are already in stage III, which is the final stage before approval. The Human Genome Project was just completed in 2003 and we are on the leading edge of the biotech revolution that will produce treatments for scores of illnesses. It would be a mistake at this exciting time in biotechnology research to do anything to inhibit innovation in this young and promising industry.

- **Congress has already recognized the need for up to 14 years to recover R&D costs.** In 1984, Congress determined that providing patent term restoration up to 14 years of effective patent life was appropriate to give innovator companies the proper incentives to spend the hundreds of millions of dollars on R&D that it takes to bring a new therapy to market.[65] The cost of bringing a biotech medicine to market is three times more expensive than in 1984 when adjusted for inflation. Medical discovery has become more difficult, more complex and more expensive since the Hatch-Waxman scheme was adopted. Many patients are still waiting for cures. Reducing the incentive to innovate now is akin to paying for short term savings at the expense of future cures.

- **Europe recognizes the need for data exclusivity:** Europe provides up to 11 years of data exclusivity, recognizing that data exclusivity is an important means of encouraging future innovation. Biotech is a uniquely American industry and we lead the world in

[60] The Lewin Group, "Saving Lives, Saving Money: Dividends for Americans Investing in Alzheimer's Research" (2004).
[61] Pharmaceutical Research and Manufacturers of America, 2006 Survey, "Medicines in Development for Neurological Disorders: Pharmaceutical Companies Developing 241 Medicines for Neurological Disorders."
[62] American Cancer Society, "Cancer Facts and Figures 2007," available at http://www.cancer.org/downloads/STT/CAFF2007f4PWSecured.pdf (last visited May 2, 2008).
[63] Schulman, K.L. & Joseph Kohles, "Economic Burden of Metastatic Bone Disease in the U.S.," Cancer vol. 109, no. 11 (June 1, 2007).
[64] See Clinical Trials.gov, available at http://clinicaltrials.gov/ct2/results?flds=Xe&flds=a&flds=b&flds=c&recr=Open&cond=metastatic+bone+disease&fund=2&show_flds=Y (last visited April 30, 2008).
[65] The House Report accompanying the Hatch-Waxman amendments noted that "by providing up to fourteen years of market exclusivity, the Committee expects 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).

biotech employment and R&D investment. It remains to be seen if the data exclusivity provided by Europe is adequate to foster biotech innovation but it is instructive that the data exclusivity offered by this competitor is more than double that provided under the Hatch-Waxman generic drug scheme.

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?***

A recent study conducted at Duke University examined the "breakeven" times of new biologic drugs. The breakeven time is defined as the time necessary for a biologic to earn a positive and risk-adjusted return on the upfront investment made in its research and development. The study in question analyzed a model portfolio of biotech products with sales that are representative of the actual historical distribution.

The study found that breakeven lifetimes were **between 12.9 and 16.2 years**.[66] Any data exclusivity period proposed for innovative biologics should reflect this range of breakeven times. Based on these findings, the study's author asserted that providing only nominal data exclusivity periods would have "adverse effects" on biological innovation.

According to the study, providing little or no data exclusivity would encourage premature patent challenges by biosimilar applicants shortly after introduction of the innovative product.[67] This would add more uncertainty to the already uncertain venture of innovative drug development. Only 10% of potential drug candidates reach the human trial phase.[68] Only a small portion of that 10% actually reach the market[69] and only two out of ten marketed drugs ever produce revenues that match or exceed R&D costs.[70] If those revenues are diverted because the law fails to protect the underlying intellectual property (patents and data) and allows others to free ride on the innovators' investments, biotech R&D will suffer irreparable harm.

The majority of biotechnology companies are not profitable. In fact, as of 2006, the publicly traded U.S. biotechnology industry as a whole had not once been profitable in its 31-year history.[71] Early-stage biotechnology companies without any products on the market are wholly dependent on investors' willingness to take a risk on an uncertain promise of return. It would be imprudent to insert into legislation any provisions that would reduce this willingness.

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[66] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007).
[67] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007) at p. 30.
[68] Conaway, Carrie, "The Pros and Cons of Pharmaceutical Patents," Federal Reserve Bank of Boston, Regional Review, Vol. 13, No. 1 (Q1 2003), at p. 12.
[69] C. Conaway, "The Pros and Cons of Pharmaceutical Patents," Federal Reserve Bank of Boston, Regional Review, Vol. 13, No. 1 (Q1 2003).
[70] Vernon, J. et al., "Drug Development Costs when Financial Risk is Measured Using the Fama-French Three Factor Model," Unpublished Working Paper, January 2008.
[71] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007" (2007), at p. 17.

Excerpts from the Duke University study:

> *One approach that policymakers could follow that is based on basic economic principles would be to align data exclusivity periods with the time necessary for the representative new biologic entity to earn a positive risk adjusted return on the large upfront R&D investment. This paper presents a preliminary analysis of breakeven times for new biologicals to gain insights into this issue. In this regard, a simulation analysis was undertaken of a model portfolio of biotech products with sales that are representative of the actual historical distribution.* ***The breakeven lifetimes were found to be between 12.9 and 16.2 years*** *at alternative discount rates of 11.5% and 12.5% respectively.*[72]

> *Proposed legislation without any provisions for a data exclusivity period or only very nominal periods of exclusivity would have adverse effects for these biological innovation activities. Under these legislative scenarios, there would likely be an explosion in patent challenges shortly after a new product is introduced. The resulting uncertainty and litigation costs would increase risks and diminish R&D investment funding sources for this sector, especially for early-stage R&D in companies without any profitable products (the majority of biotech firms). As a consequence, the future introduction of important new medicines could be delayed significantly or deterred altogether. This would not be a desirable outcome for policymakers who must balance the terms of competition between innovators and imitators. It is important to avoid these unintended consequences for an industry with strong entrepreneurial roots and important expected benefits for human health and welfare.*[73]

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

Data exclusivity for second-generation products is very important in the context of a biosimilar approval pathway. These products represent important advancements for patients and must go through the same rigorous FDA approval process as the first generation product, including development and submission of full safety and efficacy data to support approval of the application. Accordingly, data exclusivity for second generation products is necessary to ensure that these types of advancements are developed and allow patients to benefit from them.

Data exclusivity is a critical component of a balanced statutory pathway for biosimilars, rendering possible biosimilar approval and availability in the market while appropriately safeguarding incentives for biotechnology innovation. Such exclusivity provides an important incentive to undertake the significant costs, time, and risks required to research, develop, test, and bring to market the extensive pipeline of treatments that can allow patients to live longer and healthier lives.

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

The need to encourage research and development of new therapies, however, does not suddenly cease with the initial approval of a biologic. Indeed, data exclusivity is also critical to providing the necessary incentive to research, develop, test and obtain FDA approval for new indications and other important developments emerging from existing biologics. For example, data exclusivity for new indications is critical in areas such as cancer research, where the initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies typically occur much later in time. Data exclusivity provides companies with the incentive to incur the significant additional time and expense required for this later research and development. In order for this innovation to thrive, and for researchers to discover future generations of existing products, robust data exclusivity must be provided. Without this incentive to continue to discover, patients may ultimately be left only with attempted copies of older medicines, rather than more advanced, targeted ones. A well-considered biosimilar regime should ensure more therapeutic options for patients, not fewer. Thus, we strongly suggest that a comprehensive biosimilar system should incentivize not only the discovery and development of new substances, but also improvements to or modifications of existing therapies.

It should also be noted that data exclusivity for innovators in any biosimilar regimen would not, as some may have suggested, operate as an extension of patent protection. Rather, the period of data exclusivity would run concurrently with the patent term for the product.

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

Patents and data exclusivity are both important tools to protect intellectual property, but they encourage innovation in different ways. Patents protect the initial invention – the molecule, or new way of making a product, and typically are issued very early in the research process, perhaps even before it can be known whether the molecule has any therapeutic or commercial potential. The patent term begins ticking away the minute the patent application is submitted to the U.S. Patent & Trademark Office (PTO) (or, for applications submitted before June 8, 1995, the date the patent is issued) – usually years before a drug company has received FDA approval to begin marketing a product.

The purpose of data exclusivity is to encourage companies to embark on the lengthy, complicated, and risky development program required for FDA approval. If successful in obtaining that approval, data exclusivity allows an innovator a period of time after FDA approval during which a generic may not rely on the valuable data developed by the innovator to gain FDA approval. Without such a period, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved.

It is important to note that data exclusivity is very different from market exclusivity. Market exclusivity means that no other manufacturer can obtain approval of the same drug, even with a full application supported by their own data (as is the case for orphan drugs). Data exclusivity

simply prevents reliance on the innovator's data for FDA approval, but does not prohibit a manufacturer from gaining approval of a product based on their own data.

The science of biotechnology makes the difference between these two tools for protecting intellectual property very important to future biotech innovation. The Hatch-Waxman model requires a generic drug (an Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents. The assumption of patent infringement that is inherent in the generic drug model may not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness". Put simply, for scientific reasons it is *impossible* to make an identical copy of a biologic medicine. Biosimilar manufacturers can be expected to claim they have "designed around" the innovator patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections – namely data exclusivity – for innovators of biotechnology products.

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

It is more useful to determine how much data exclusivity is necessary to encourage biotech innovation, than to examine whether that number is the same for both biotech and small-molecule products. Patients deserve the best and safest medicines that technology can deliver, at the most competitive prices. Congress attempted to strike a balance between these objectives when it adopted the Hatch-Waxman generic drug legislation in 1984. Whether or not parties believe five years is adequate for small-molecule products, it is clear that this period is not enough to encourage biotech innovation. The model fails to account for the development costs associated with product approval and the rationale that was used to develop the generic drug model does not apply to biotech innovation as a result of the differences between the science of chemistry and biotechnology and the maturity of the biotech and pharmaceutical industries at the time an abbreviated approval pathway was proposed for the respective industries.

First, Hatch-Waxman fails to sufficiently recognize and reward the separate and independent purposes of the patent system and the regulatory scheme of data protection and the separate investments required by the innovator to secure a patent and a clinical data set that demonstrates the safety and efficacy of the product. Patents protect the initial invention – the molecule, or new way of making a product, and typically are issued very early in the research process, perhaps even before it can be known whether the molecule has any therapeutic or commercial potential. The patent term begins ticking away the minute the patent application is submitted to the U.S. Patent & Trademark Office (PTO) (or, for applications submitted before June 8, 1995, the date the patent is issued) – usually years before a drug company has received FDA approval to begin marketing a product. Once issued, a patent provides exclusive rights to what is claimed as the invention. A large majority of the 1400 biotech companies in the U.S. are small research

companies that make inventions, file patent applications and then look to license the commercial rights to its products to other companies.

The purpose of data exclusivity, on the other hand, is to encourage companies to embark on the lengthy, complicated, and risky clinical development program required for FDA approval. The average cost of developing a biologic product through FDA approval has been estimated to be about $1.2 billion.[74] If successful in obtaining that approval, data exclusivity allows an innovator a period of time after FDA approval during which a generic may not rely on the valuable data developed by the innovator to gain FDA approval. Without such a period, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved.

It is important to note that the protection conferred by data exclusivity is different from that provided by a patent. A patent would prevent another manufacturer from marketing the same drug, even with a full application supported by its own data. Data exclusivity simply prevents reliance on the innovator's data for FDA approval, but does not prohibit a manufacturer from gaining approval of a product based on their own data.

Second, the balancing of interests under Hatch-Waxman was based on the ease of generic applicants in showing structural identity of the generic product to the innovator's product. The Hatch-Waxman model requires a generic drug (an Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents. The assumption of patent infringement that is inherent in the generic drug model may not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness". Put simply, for scientific reasons it is *impossible* to make an identical copy of a biologic medicine. Biosimilar manufacturers can be expected to claim they have "designed around" the innovator patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections for innovators of biotechnology products.

Finally, the field of biotechnology is immature compared to the traditional small-molecule drug market at the time of the Hatch-Waxman legislation. In 1984, when the Hatch-Waxman amendments were passed, there were tens of thousands of marketed drug products, many of which had been safely used for dozens of years. FDA, the medical community, and the public had decades of experience with these products. By contrast, today there are only about 155 approved biotechnology products, most of which were approved very recently.[75] Only 20 or 30

[74] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008). Hatch-Waxman preserved 5 years of data exclusivity for innovative small molecule drugs to recoup the $397 million (adjusted to 2005 dollars) it cost then to develop a new drug.
[75] Biotechnology Industry Organization, "Biotechnology Industry Statistics," available at

of the 1400 U.S. biotech companies have turned a profit. Moreover, the cost to develop a new biological therapy today is estimated at $1.2 billion, an increase of three times what it cost to develop a drug back in 1984.[76] The biotech industry is vulnerable to market instabilities and maintaining an incentive structure that promotes investment in uncertain research and development is essential to the future of this U.S. industry, and finding cures for patients.

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

Patents should not be the principal form of intellectual property protection for biotechnology. Both patent protection and data exclusivity are both important and necessary tools for encouraging innovation in the biotechnology and pharmaceutical industries. These tools should be tailored to the realities of today's marketplace today in order to ensure that future cures are not compromised by interest in short term savings.

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?***

Patents and data exclusivity are both important means of encouraging investment in biotechnology but they serve different roles. A period of at least 14 years of data exclusivity in any biosimilar bill is essential for continued biotech innovation.

Strong protection of intellectual property – both patents and data – is the cornerstone of any research-intensive, innovation-driven industry. Failure to provide adequate intellectual property protection will undermine investment in biotech innovation. Venture capital that is the lifeblood of startup companies will divert resources to investments with more certain returns, regardless of their social value. Investment decisions by more mature biotech companies that are self-funding are necessarily driven by the possibility of recovering the cost of bringing a product to market because this funds the next discovery. Without adequate intellectual property protection, research and development will be greatly diminished. This is a very expensive proposition for patients waiting for cures. We know that incentives to invest can be successful. Both pediatric studies and orphan drug development have been significantly stimulated by intellectual property protections put in place by Congress. Moreover, partnerships with American universities on high-risk early-stage research would be severely hindered.

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http://www.bio.org (last visited April 18, 2008).

[76] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008). Hatch-Waxman preserved 5 years of data exclusivity for innovative small molecule drugs to recoup the $397 million (adjusted to 2005 dollars) it cost then to develop a new drug.

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.***

Science and safety considerations, rather than the economics of biosimilars, must drive the policy decisions that surround the implementation of an abbreviated approval pathway for biosimilars. As a result of the difference in the science of biotechnology and traditional pharmaceuticals, the market dynamic and any associated savings from biosimilars is likely to be far different from the generic model that consists of heavy discounting and rapid uptake of generics. In fact, credible savings estimates are modest over a ten-year time period.

To date, a number of organizations have tried to quantify the savings potential from creating a biosimilar pathway. Most of these modeling attempts focus on estimating the timing of biosimilar entry, market uptake, and discounting levels, because these are the key drivers that influence the level of savings that will ultimately be available to consumers. The results of this research indicate that savings opportunities from creating a biosimilar pathway will be very different from the savings opportunities created from the Hatch-Waxman generic drug law in 1984.

Three studies that have done a credible and rigorous job of quantifying the impact of biosimilar entry into the market place are those conducted by Avalere Health, LLC, Henry Grabowski, Ph.D, and Howrey/CAP. Avalere Health, LLC, in its "CBO-style" estimate, calculated $3.6 billion in Federal savings over 10 years.[77] Henry Grabowski, Ph.D. simulated market entry rates and corresponding price discount levels and predicted that savings would be closer to or below Avalere's calculated savings estimate than other higher estimates, although he did not provide a specific number.[78] Howrey/CAP reviewed the assumptions made by the Pharmaceutical Care Management Association (PCMA) and Express Scripts studies and re-estimated savings at between $2.0 to $2.8 billion over a 10-year time period.[79]

These estimates are credible because they address, using different methodologies and approaches, the key components needed to assess any potential cost savings. Importantly, these studies taken collectively examine the implications that the complex nature of biotechnology has on the number of biosimilar competitors, which is then reflected in product pricing levels, the

[77] Avalere Health, LLC, "Modeling Federal Cost Savings from Follow-on Biologics," (April 2007), at p. 10.
[78] Grabowski, Henry, et al., "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), at pp. 1-7, available at http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (last visited April 18, 2008).
[79] Howrey LLP, CAP Analysis & PhRMA, "The Inflated Projections of Potential Cost Savings from Follow-On Biologics: An Analysis of the Express Scripts and Engel & Novitt Reports" (May 2007), at p. 6, available at http://www.howrey.com/files/News/6efa58d8-75a8-49e0-ac0f-512f45769c77/Presentation/NewsAttachment/13ce02b8-b57f-4f2f-b682-4d79c22d578a/Biologics%20White%20Paper%205-2-07.pdf (last visited April 18, 2008). at pp. 2-3.

time lag between passage of a bill and promulgation of regulations and guidance, and the market uptake rates for biosimilar products.

Product pricing and market uptake will play important roles in assessing the potential cost savings if a biosimilar pathway is established. As these reports note,[80] the price of biosimilar products is likely to be close to that of the innovator product for several reasons. Biotech products are much more difficult and expensive to produce than most pharmaceuticals and often have higher fixed costs. Consequently, there will be far fewer biosimilar entrants than is usually seen with small-molecule generics.[81] The combination of these factors will make it very unlikely that biosimilar products will bring about the price differential that generic products do. Most estimates predict savings of 10 to 25 percent, a savings range in line with the Generic Pharmaceutical Association's (GPhA) own expectations.[82] In fact, one biosimilar product on the market – Omnitrope® (somatropin recombinant) – has, according to the investment firm Griffiths McBurney, seen discounting levels of 20% to 25% in Germany, and 10% to 20% in the Australian human growth hormone market.[83] This is consistent with a report from Wachovia Capital Markets (10-20% discount).[84]

In recent testimony before the House Oversight and Government Reform Committee, Dr. Grabowski concluded that:

> Based on our analyses, we conclude that the costs of entry will be significantly higher for follow-on biologics than generic drugs. As a consequence, we expect fewer firms will enter, and average prices will decline less for follow-on biologics than generic drugs. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the government programs and other payers.[85]

The science of biotechnology also has implications for market uptake. Market uptake for biosimilars will likely be gradual, meaning any potential savings will not materialize until years from now. The limited clinical information that is likely to have been presented at the time of

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[80] Avalere Health, LLC, "Modeling Federal Cost Savings from Follow-on Biologics," (April 2007), at p. 8, available at http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf (last visited April 18, 2008); Grabowski, Henry, et al., "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), at p. 7, available at http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (last visited April 18, 2008); Howrey LLP, CAP Analysis & PhRMA, "The Inflated Projections of Potential Cost Savings from Follow-On Biologics: An Analysis of the Express Scripts and Engel & Novitt Reports" (May 2007), at p. 6, available at http://www.howrey.com/files/News/6efa58d8-75a8-49e0-ac0f-512f45769c77/Presentation/NewsAttachment/13ce02b8-b57f-4f2f-b682-4d79c22d578a/Biologics%20White%20Paper%205-2-07.pdf (last visited April 18, 2008).

[81] Grabowski, H. et al., "Entry and Competition in Generic Biologics," Managerial and Decision Economics, 28: 439-451 (2007), at p. 449.

[82] GPhA, Press Release (Feb.14, 2007), available at http://www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=3202 (last accessed April 29, 2008).

[83] Ordonez, C. & T. Connolly, "Accretropin Receives FDA Approval," Griffiths McBurney (Jan. 25, 2008).

[84] Farmer G. et al., "Biogen Idec, Inc. BIIB: Shares unjustifiably rich on acquisition speculation," Wachovia Capital Markets LLC (Oct. 10, 2007).

[85] Statement of Henry Grabowski, Ph.D., Duke University, before the House Oversight and Government Reform Committee, March 26, 2007.

FDA approval may impact the readiness of physicians and patients to consider use of these products.[86] Furthermore, a lack of experience of bringing branded products to market by biosimilar manufacturers could also slow uptake of biosimilars.

Sales data reported by IMS and manufacturers show that Omnitrope®'s uptake in Australia (product launched in November 2005), the European Union (product authorized for marketing in April 2006), and the United States (product launched in March 2007) has been minimal. For example, a report of January 2008 sales data in the U.S. showed that Omnitrope® had no more than a 1.5% market share of prescription renewals (TRx).[87]

Several published estimates of the savings from biosimilars that are significantly higher than the Avalere, Grabowski and Howrey studies have used unrealistic assumptions around the timing of biosimilar entry, uptake rates, current innovator biologic patent expiry, and discounting levels.

BIO has critiqued two of these studies (released by the PCMA and Express Scripts) that claimed large savings from a biosimilars pathway.[88] BIO determined that those studies overestimated the savings due to, among other things:

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

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?***

Over the past ten years, Amgen has spent an average of 21.7% of its total revenues on research and development of biologic medicines. This translates to nearly $17 billion spent on research and development of innovative therapies.[89]

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[86] Grabowski, Henry, et al., "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), at pp. 1-7, available at http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (last visited April 18, 2008).

[87] Sinclair, A. and K. Scotcher, "Novo Nordisk: Initiating coverage with underweight and TP of DKK305," HSBC Global Research (March 27, 2008).

[88] Biotechnology Industry Association, "Recent Studies of Follow-on Biologics Are Based on Seriously Flawed Assumptions," (Feb. 22, 2007), available at www.bio.org/healthcare/followon/20070222.pdf (last visited May 1, 2008).

[89] Totals and averages for 1997-2007 calculated from: Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 1998 (filed March 16, 1999); Amgen Inc., Form 10-K405 For the Fiscal Year Ended December 31, 1999 (filed March 7, 2000; Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2000 (filed March 7, 2001); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2001 (filed Feb. 26, 2002); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2002 (filed March 10, 2003); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2003 (filed March 11, 2004); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2004 (filed March 9, 2005); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2005 (filed March 10, 2006); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2006 (filed Feb. 28,

Generally speaking, the average cost of developing a biologic medicine is $1.2B.[90] The long-term savings to the healthcare system from this investment in the development of innovative therapies is significant. Finding treatments for currently incurable illnesses could save payers billions.

For example, if the biotechnology industry successfully brings to market even just one medicine that can delay the onset, or slow the progression of, Alzheimer's disease by five years, Medicare and Medicaid could save $100B in annual costs by 2020.[91]

The National Institutes of Health has estimated that, in 2006, $78.2B was spent on total direct medical costs for cancer.[92] In 2004, the national cost burden for patients with metastatic bone disease (MBD) was estimated at $12.6B.[93] This means that, even if a cure is found for no other cancer except MBD, 17% of the total direct medical cost for cancer could be eliminated. There are currently 14 industry-sponsored studies actively recruiting patients with metastatic bone disease.[94] Four of these trials are already in stage III, which is the final stage before approval.

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

The implications of a pathway for the approval of biosimilars for United States economic competitiveness depend upon the provisions of the law. The U.S. leads the world in biotech investment and biotech jobs. In 2003, the U.S. biotechnology industry spent more than $14 billion on research and development, more than double the amount of biotech industry R&D spending in Germany, France, Canada, Denmark, Switzerland, Italy, Australia, Israel, and Korea combined.[95] Employment figures also reflect the U.S.'s dominance in biotech R+D: the Organization for Economic Co-operation and Development estimates that the U.S. biotech sector employed about 73,000 people in 2003 – compared to 46,000 biotech employees in the U.K., Germany, France, Canada, Denmark, Switzerland, Israel, Spain, Sweden and Belgium combined.[96] Other studies estimate the U.S. jobs figure much higher (see statistics below).

2007); Amgen Inc., Form 10-K For the Fiscal Year Ended December 31, 2007 (filed Feb. 28, 2008), available at http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-sec&control_selectgroup=Annual%20Filings (last visited May 1, 2008).

[90] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008).

[91] The Lewin Group, Saving Lives, Saving Money: Dividends for Americans Investing in Alzheimer's Research (2004).

[92] American Cancer Society, "Cancer Facts and Figures 2007," available at http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf (last visited May 2, 2008).

[93] Schulman, K.L. & J. Kohles, "Economic Burden of Metastatic Bone Disease in the U.S.," Cancer vol. 109, no. 11 (June 1, 2007).

[94] See Clinicaltrials.gov, available at http://clinicaltrials.gov/ct2/results?flds=Xe&flds=a&flds=b&flds=c&recr=Open&cond=metastatic+bone+disease&fund=2&show_flds=Y (last visited April 14, 2008).

[95] Van Beuzekom, Brigitte and Anthony Arundel, "OECD Biotechnology Stats – 2006," at p. 41.

[96] Van Beuzekom, Brigitte and Anthony Arundel, "OECD Biotechnology Stats – 2006," at p. 21.

Therefore, any law that undermines the future of biotechnology will have significant implications for the U.S. economy, and certainly more than any other national economy.

A more recent snapshot of the U.S. biotechnology industry shows:

- Employed a total of 180,800 people in 2006 – a 6% increase in employment over 2005[97]
- Is one of the most research-intensive industries in the world, spending $19.8 billion on R&D in 2005[98]
- The top five biotech companies invested an average of $130,000 per employee in R&D[99]
- In 2001, 884 U.S. firms reported biotechnology R&D expenditures of PPP$ $16.4 billion, representing about 10% of all U.S. industry R&D in that year[100]

In 2006, out of 1,452 biotechnology companies in the U.S., only 336 were publicly traded[101] and only 20 were profitable.[102] A BIO survey of 300 small biotech companies showed that:

- 40% reported company revenue from all sources in the preceding year LESS THAN $150,000[103]
- 66% had annual revenues LESS THAN $1 MILLION[104]
- The only revenues for the vast majority of the companies consisted solely of milestone and royalty payments[105]
- FEWER THAN 10% of the surveyed companies had any products on the market[106]

[97] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007," (2007) at p. 8.
[98] Biotechnology Industry Organization, "Biotechnology Industry Facts," available at http://bio.org/speeches/pubs/er/statistics.asp (last visited May 2, 2008).
[99] Biotechnology Industry Organization, "Biotechnology Industry Facts," available at http://bio.org/speeches/pubs/er/statistics.asp (last visited May 2, 2008).
[100] Van Beuzekom, Brigitte and Anthony Arundel, "OECD Biotechnology Stats – 2006," available at http://www.oecd.org/dataoecd/51/59/36760212.pdf (last visited May 2, 2008), at p. 136.
[101] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007" (2007) http://www.ey.com/Global/assets.nsf/International/Industry_Biotechnology_Beyond_Borders_2007_Full/$file/BeyondBorders2007.pdf (last visited May 2, 2008), at p. 17.
[102] Biotechnology Industry Organization, "A follow-on Biologics Regime Without Strong Data Exclusivity Will Stifle The Development of New Medicines," available at http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf (last visited May 2, 2008), at p. 6, note 17.
[103] Biotechnology Industry Organization, "A follow-on Biologics Regime Without Strong Data Exclusivity Will Stifle The Development of New Medicines," available at http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf (last visited May 2, 2008), at p. 7.
[104] Id.
[105] Id.
[106] Id.

In contrast, most of the companies hoping to sell biosimilars in the U.S. are based overseas:

BASED IN CHINA	BASED IN INDIA	BASED IN KOREA
• Shanghai CP Guojian Pharmaceutical Co. • Shanghai Celgen Biopharmaceutical • Hangzhou Jiuyuan Gene Engineering Co. • Hisun Pharmaceutical • 3SBio (Shenyang Sunshine Pharmaceutical Company) • Amoytop Biotech • Anhui Anke Biotechnology • Dongbao Group	• Biocon • Dr. Reddy's Laboratories • Intas Pharmaceuticals • Ranbaxy Laboratories • Reliance Life Sciences • Wockhardt • Claris Lifesciences	• LG Lifescience • Green Cross
BASED IN SWITZERLAND	**BASED IN ISRAEL**	**BASED IN CANADA**
• Sandoz International GmbH	• Teva Pharmaceutical Industries	• Cangene
BASED IN THE UNITED STATES		
• Barr Pharmaceuticals (Montvale, NJ) (biosimilars to be manufactured through Croatian subsidiary PLIVA) • Hospira, Inc. (Lake Forest, IL) • Insmed (Richmond, VA) • Momenta Pharmaceuticals (Cambridge, MA)		

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

Patents and data exclusivity are both important forms of intellectual property. A strong patent enforcement mechanism and adequate data exclusivity will be essential to encouraging continued robust investment in biotechnology and the development of biotech medicines. To this end, any regulatory pathway for the approval of biosimilars should facilitate timely resolution of patent disputes prior to allowing any biosimilar product to come to market. This will help provide the requisite level of certainty for investors – those who commit venture capital to the development of innovative biologics, as well as those who invest in biosimilar products – to foster the growth of both the innovator and biosimilar industries.

It is important that the litigation provisions for early patent resolution be designed in a way that encourages resolution of all questions of patent validity and infringement in a timely manner but avoids wasteful, costly and unnecessary disputes that simply function to harass responsible manufacturers on both sides of the process. A litigation scheme that effectively balances the interests of both the patent holder and the patent challenger will enjoin infringement after a patent is found to be valid and infringed.

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?

If Congress fails to put in place adequate incentives to innovate, the ability of the biotechnology industry to research and develop new cures, and to deliver them to patients, will be greatly diminished. The biotech industry is very resource-intensive. It takes, on average, 12 years and

$1.2 billion to bring a biotech medicine to patients.[107] Success is the exception rather than the rule and 40% to 50% of candidates fail in Phase III studies.[108] The vast majority of biotechnology companies are not profitable today and are highly dependent on the flow of venture and investment capital to complete the research needed to bring their first product to the marketplace over a decade later. To remove or undermine incentives for new research and development now would represent a terrible blow to public health and to the patients who are waiting for treatments and cures.

Companies must make investment decisions on a regular basis. If intellectual property protection is lacking, venture capitalists will weigh that added risk with the already unlikely odds that a biotech company will be able to get a biotech product through the rigorous FDA approval process. Without this capital investment, universities will no longer be able to license their basic research discoveries to biotech companies, which, in turn, will not be able to invest in the long research and development process needed to convert that basic research into meaningful and useable treatments for patients.

According to economist Henry Grabowski of Duke University:

> Proposed legislation without any provisions for a data exclusivity period or only very nominal periods of exclusivity would have adverse effects for these biological innovation activities. Under these legislative scenarios, there would likely be an explosion in patent challenges shortly after a new product is introduced. The resulting uncertainty and litigation costs would increase risks and diminish R&D investment funding sources for this sector, especially for early-stage R&D in companies without any profitable products (the majority of biotech firms). As a consequence, the future introduction of important new medicines could be delayed significantly or deterred altogether. This would not be a desirable outcome for policymakers who must balance the terms of competition between innovators and imitators. It is important to avoid these unintended consequences for an industry with strong entrepreneurial roots and important expected benefits for human health and welfare.[109]

[107] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008).
[108] See "Deconstructing De-risking," BioCentury (June 7, 2004) (discussing risks associated with biotechnology research and development).
[109] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), at p. 30, available at http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007).

European Model (abbreviated approval pathway)

1. ***The European Union (EU) regulatory system for biosimilars requires the development of product-specific guidances which detail the standard for approval that would need to be met by a biosimilar in a defined product class. Do you think these guidances would provide similar benefits to industry, healthcare providers, and patients in the U.S.?***

The European Union's biosimilar legislation required the issuance of detailed guidelines describing the data necessary to support marketing authorizations for biosimilar products. European authorities have since formally adopted guidelines, which were drafted with substantial public and industry input. Specifically, the European Medicines Agency (EMEA) issued concept papers (with a period for the public to submit comments), then draft guidelines (with a period for the public to submit comments), and then separate product-specific guidelines (with a period for the public to submit comments). The final guidelines entered into effect approximately six months after their final adoption.[110] All of the EU biosimilar guidelines were developed using a transparent and public process, involving consultations of all stakeholders. The EMEA has also published an overview of all comments on the guidelines and explained the rationale behind the EMEA's acceptance or non-acceptance of the points made in consultation.

Contrary to criticism that adopting such a guidance development process in the U.S. would take too long, the European experience shows otherwise: guideline development from start to finish took less than two years.

Industry, healthcare providers, and patients would clearly benefit should a comparable approach be adopted in the United States. The issue of biosimilars raises very complex scientific and regulatory issues that should be addressed in regulations or guidance. Scientific experts and other interested stakeholders should therefore have an opportunity to comment on the development of appropriate approval standards. As the U.S. Food and Drug Administration (FDA) has acknowledged, it should have the most current and most relevant scientific information available to it before setting any regulatory standards by which biosimilar applications will be considered. By defining these standards for approval in formal guidance documents after seeking public comment from experts in the area, FDA will not only provide consistent standards for biosimilar manufacturers to meet, the agency will also generate confidence in the biosimilar approval process among healthcare providers and patients, and meet the legitimate expectation that the agency will first define the relevant standards and then assess applications in light of such standards. Moreover, the European approach provides a good model for – and reflects the important advantages of – engaging in a public and transparent guidance development process.

By promoting the development of guidance and doing so in a public and transparent manner, FDA will be able to receive valuable input from healthcare providers and patients – who are the ultimate end-users of innovator biologics and who have the most real-world, clinical experience in their use. By ensuring that healthcare providers and patients have a meaningful opportunity to

[110] See, e.g., European Medicines Agency, "Guideline on Similar Biological Medicinal Products," CHMP/437/04, (Sept. 2005), at ¶¶ 1.1, 1.2, 1.3 (noting that specific guidelines will give information about the scientific data to be provided in an application for a similar biological medicinal product).

contribute to the development of biosimilar approval standards, FDA will be instilling greater confidence in the stakeholders who have the greatest interest in ensuring the safety of biosimilars in the United States – patients and their physicians These groups will be familiar with, and have confidence in, the standards for approval which a newly-approved biosimilar would be required to meet, if they themselves were involved in the very development of those standards.

By defining product class-specific guidances (*e.g.* for erythropoietins, insulins, growth hormones, etc.) physicians and patients will know that *any* newly-approved biosimilar in the relevant class will have met a certain, defined standard criteria for approval.

Without such a defined standard in the form of a product class-specific guideline, biosimilar applicants would negotiate their own individual approval standards with FDA, involving different clinical data sets and acceptance criteria. Such a case-by-case approach would not only create inconsistency in approval standards, but it would increase the need for physicians and patients to review each newly-approved biosimilar on its own merits – as each approved biosimilar could be more or less "similar" to the innovator biologic, supported by different data in different patient populations.

As Dr. Janet Woodcock, then serving as FDA's Chief Medical Officer, stated before the Energy and Commerce Committee of the U.S. House of Representatives: "[I]t is very important in this area, follow-ons, that we stay up to date with the science and therefore we have a dynamic public process that keeps giving us the scientific input that we need."[111]

It is essential that FDA undertakes a thoughtful, deliberate, and transparent assessment of the scientific and regulatory standards for approval of biosimilar products and that the agency solicits input from the public before developing regulations and product class-specific guidances. Requiring the development of guidances detailing the approval standards will not only promote consistency in biosimilars, it will also increase the medical community's and patients' confidence in approved biosimilar medicines.

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?***

   "U.S. policy should be guided by the recognition around the world that data exclusivity is an important form of intellectual property protection. It remains to be seen whether the 11 years of data protection provided by Europe will be adequate to foster continued investment in research and development in biotechnology. Economic studies in the United States suggest that 11 years falls

[111] Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration, before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007.

short of the time needed for many products to recover the cost of development."[112]

Although European legislation allows for up to 11 years of data exclusivity, in the United States a more appropriate exclusivity period of at least fourteen years should be adopted, for several reasons. First, a fourteen year exclusivity period would ensure that the United States retains its worldwide lead in biotechnology innovation. To remain the most attractive regulatory environment for biotechnology, the U.S. must offer better incentives for biotechnology research and development than the European Union (EU). The fourteen year period of exclusivity would distinguish the U.S. from the EU and promote a strong biotechnology industry in this country.

Second, a fourteen year period of data exclusivity finds support in the policy underlying the patent term restoration provisions of the 1984 "Drug Price Competition & Patent Term Restoration Act",[113] commonly referred to as the Hatch-Waxman Act. Unlike innovators in other industries, pharmaceutical and biotechnology innovators may lose a substantial amount of their 20-year patent term to the research and development process and the FDA application review process. Recognizing the impact of this shortened effective patent life on incentives to innovate, Congress in 1984 permitted partial patent term restoration, capping the restored effective patent life at fourteen years. The House Report for the Hatch-Waxman amendments indicates that Congress selected the fourteen year period so that "research intensive companies will have the necessary incentive to increase their research and development activities."[114]

Third, the expense, risk, and length of the research and development and FDA approval phases have increased since 1984, even for small-molecule drugs – and they are likely even longer for the newest biotechnology products.

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?

Undermining biotech innovation will have a direct impact on United States competitiveness. The U.S. leads the world in biotechnology research and development. In 2006, the U.S. biotech industry invested in R&D nearly four times what the next largest market spent.[115] That translates into U.S. jobs. Economic research makes clear that data exclusivity is important to foster future biotech innovation. If biotech innovation is stunted because intellectual property is not adequately protected, our economy will be negatively affected. At a time when countries around the world are courting clean industries that bring with them high-skilled and well-paying jobs, it would be very short sighted of the U.S. to do the opposite. Failure to provide adequate innovation incentives could diminish what is now a vibrant U.S.-based industry.

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[112] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), available at http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007).
[113] P.L. 98-417, "Drug Price Competition and Patent Term Restoration Act of 1984" (Sept. 24, 1984).
[114] H.R. Rep. No. 98-857, at 41 (1984).
[115] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007," available at: http://www.ey.com/Global/assets.nsf/International/Industry_Biotechnology_Beyond_Borders_2007_Full/$file/BeyondBorders2007.pdf (last visited May 2, 2008), at p. 7.

4. ***To what extent do you agree or disagree with the EU's current model when it comes to access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for the approval of a new product? What are the advantages and disadvantages of the EU's model? Are there other models that the U.S. can examine? If yes, what are the strengths and weaknesses of their models?***

Europe grants 11 years of data exclusivity to innovative products. This works in conjunction with – not in addition to – the unlimited patent term restoration granted in Europe in order to establish comprehensive intellectual property rights that allow innovators an opportunity to recover the cost of investing in risky research and development. The actual number of years of data exclusivity provided to biotech products under a U.S. biosimilar scheme should be guided by an analysis of the amount of time it takes for a successful product to "break-even" on research and development resources invested. Economist Henry Grabowski found that number to be between 12.9 and 16.2 years.[116] Consequently, a data exclusivity period of 14 years would be appropriate for a biosimilar regime in the United States.

The European Union's model has several advantages:

- It provides for up to 11 years of data exclusivity
- The generic model is not applied to biosimilars
- It follows a science-based and public process in developing regulatory standards for approval
- It calls for the development of product class-specific guidance for biosimilars, which will ensure consistency in approval standards
- It requires that clinical data be provided in support of biosimilar applications, ensuring adequate demonstration of similar efficacy, safety, and immunogenic potential before approval
- It does not call for the European Medicines Agency (EMEA) to make therapeutic equivalence determinations

There are no overt disadvantages with the EU model that need to be noted as biosimilars legislation is developed in the U.S.

Australia, Canada, Switzerland, Saudi Arabia, and the World Health Organization all have developed formal legal and/or regulatory frameworks for the approval of biosimilars. It should be stressed that these countries/organizations have created frameworks that provide for an appropriate standard of similarity, in contrast with some other countries – for example, in Asia – where there are copies of innovator biologics on the market and questionable standards of similarity being accepted.

Without going through each country in detail, the nations mentioned above have each, for the most part, created a model that is broadly similar to that created by the European Union.

[116] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), available at http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007). (emphasis added).

- The Swiss regulatory agency (Swissmedic) fully refers to the EMEA's guidelines, but also includes some Swiss-specifics provisions.[117]

- The Australian regulatory agency (Therapeutic Goods Administration) has adopted the full series of EMEA guidelines into their national regulatory regime with no changes.[118]

- The World Health Organization (WHO) is developing its own draft regulatory guideline[119] for biosimilars (referred to as "subsequent entry biologics"). The draft guidance document was developed by a working party of global regulators (including the U.S. FDA) and was issued for comment in April 2008. The draft guidance does not adopt the EMEA guidelines "word-for-word", as do the Switzerland and Australia regulatory agencies, but is closely mirrors the EMEA's approval standards for biosimilars.

- The Canadian regulatory agency (Health Canada) issued a draft guidance document[120] regarding "subsequent entry biologics" in January 2008. As with the WHO draft guidance, this is not a "word-for-word" adoption of the EMEA guidelines, but it closely mirrors the EU standards for approval of biosimilars.

- Saudi Arabia has created an approval pathway[121] that relies on a system of "drug master files." This model differs from those in the other countries described herein; however, this model serves to establish a similar standard whereby clinical data are required in order to support approval of biosimilars.

In summary, a number of countries and authorities that have undertaken a thorough assessment in establishing legal and regulatory standards for approval of biosimilars have all settled on models that, for all intents and purposes, replicate the standards established by the European Union.

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[117] See generally http://www.swissmedic.ch/?lang=2 (last visited May 1, 2008).
[118] See, e.g., Australia Therapeutic Goods Administration, "EU Guidelines Adopted in Australia: Comparability/Similar Biological Medicinal Products," available at http://www.tga.gov.au/docs/html/euguide/euad_nonc.htm (last visited May 1, 2008).
[119] World Health Organization, "Guidance on International Nonproprietary Names," available at http://www.who.int/medicines/services/inn/innquidance/en/index.html (last visited April 17, 2008).
[120] See Health Canada, "Consultation on Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)" (March 14, 2008), available at http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/consultation/seb-pbu/index_e.html (last visited May 1, 2008).
[121] See Saudi Arabia Food & Drug Authority, "Drug Master Files for the Registration of Biosimilars: First Draft," (Aug. 2008) available at http://www.sfda.gov.sa/NR/rdonlyres/CB6114FE-6503-4CD8-87CE-74215929A2B3/967/DrugMasterFileRequirementsforRegistrationofBiosimi.pdf (last visited May 1, 2008).

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

The EU experience provides the most reliable source of clinical experience for biosimilars, as historical FDA decisions for proteins, with the exception of Omnitrope® (somatropin recombinant) are not necessarily relevant. However, as the biosimilars approved in the EU have only been on the market for a short period of time, it is not possible to tell if there are any safety or efficacy problem that are appearing after approval or if they are in any way different from that seen with the innovator biologics.

To date, there have been nine separate biologics that have completed the European Medicines Agency (EMEA) review process. Four of these (two growth hormones and two erythropoietins) have been approved,[122] one (interferon alfa-2a) has been rejected,[123] and three (soluble insulin, isophane insulin and biphasic insulin) were withdrawn by the applicant[124] prior to rejection. Another product (granulocyte-colony stimulating factor) has been granted a positive opinion by the EMEA,[125] but formal approval by the European Commission is pending.

In each of these cases, clinical data were necessary in order to support the decision reached by the EMEA, because a conclusion could not be reached based on the biophysical data alone. Naturally, the approved biosimilars had demonstrated that, while there were biophysical

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[122] See European Medicines Agency, "European Public Assessment Report for Omnitrope" (April 12, 2006), available at http://www.emea.europa.eu/humandocs/Humans/EPAR/omnitrope/omnitrope.htm (last visited May 1, 2008); "European Public Assessment Report for Valtropin" (April 24, 2006) available at http://www.emea.europa.eu/humandocs/Humans/EPAR/valtropin/valtropin.htm (last visited May 1, 2008); "European Public Assessment Report for Retacrit" (Dec. 18, 2007), available at http://www.emea.europa.eu/humandocs/Humans/EPAR/retacrit/retacrit.htm (last visited May 1, 2008); "European Public Assessment Report for Binocrit" (Aug. 28, 2007), available at http://www.emea.europa.eu/humandocs/Humans/EPAR/binocrit/binocrit.htm (last visited May 1, 2008).

[123] See European Medicines Agency, "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007), available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RAR-en.pdf (last visited May 1, 2008).

[124] See European Medicines Agency, "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008), available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/31777807en.pdf (last visited May 1, 2008); "Withdrawal Assessment Report for Insulin Human Long Marvel (International Nonproprietary Name: Isophane Insulin Injection)," Procedure No. EMEA/H/C/000846 (published March 19, 2008), available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/7034908en.pdf (last visited May 1, 2008); "Withdrawal Assessment Report for Insulin Human 30/70 Mix Marvel (International Nonproprietary Name: Biphasic Insulin Injection)," Procedure No. EMEA/H/C/000847 (published March 19, 2008), available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/701790en.pdf (last visited May 1, 2008).

[125] See European Medicines Agency, Committee for Medicinal Products for Human Use, "Summary of Positive Opinion for Tevagrastim (International Non-proprietary Name (INN): filgrastim)," EMEA/CHMP/67459/2008 (Feb. 21, 2008), at p. 1 ("Summaries of positive opinion are published without prejudice to the Commission Decision, which will normally be issued within 67 days from adoption of the Opinion."), available at http://www.emea.europa.eu/pdfs/human/opinion/Tevagrastim_6745908en.pdf (last visited May 1, 2008).

differences between the biosimilar and the innovator, those differences were found proved to have no significant clinical consequences as proven by the clinical studies.

However, for the four biosimilars that were rejected or their applications withdrawn, clinical studies demonstrated that their safety and efficacy were not similar to the innovator – that is, there were clinically meaningful differences that were not predicted by the analytical or animal studies:

- In the case of the rejected interferon alfa-2a, which is used to treat hepatitis C, patients receiving the biosimilar were between 2 and 3 times more likely to have the disease return after an initial response.[126] Furthermore, the patients receiving the candidate biosimilar interferon were more likely to experience an adverse event.[127]

- In the case of the withdrawn insulins, which are used to control blood sugar levels in patients with diabetes, it was demonstrated that all three of the candidate biosimilars could not control diabetes in a similar way as the innovator insulins. One of the three insulins could potentially induce a blood sugar lowering effect 45% higher than the innovator insulin,[128] which is clearly not clinically acceptable nor, indeed, similar to the innovator. In addition, patients with type I diabetes who received the candidate biosimilar insulins were twice as likely to experience an adverse event.[129]

At this point in time it is premature to make a judgment about the post-market safety and efficacy of Omnitrope®; however, in pre-market testing, patients in clinical studies of Omnitrope® did experience problems.

In the studies supporting approval of Omnitrope® in both the U.S. and Europe (and Australia) patients (children with growth deficiency) did experience a significant immunogenicity problem

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[126] European Medicines Agency, "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007), at pp. 20-22, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RAR-en.pdf (last visited May 1, 2008).

[127] European Medicines Agency, "Refusal Assessment Report for Alpheon (International Nonproprietary Name: recombinant human interferon-alfa-2a)," Procedure No. EMEA/H/C/000585 (published Oct. 22, 2007), at p. 28, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RAR-en.pdf (last visited May 1, 2008).

[128] European Medicines Agency, "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008), at p. 16, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/31777807en.pdf (last visited May 1, 2008).

[129] European Medicines Agency, "Withdrawal Assessment Report for Insulin Human Rapid Marvel (International Nonproprietary Name: Soluble Insulin Injection)," Procedure No. EMEA/H/C/845 (published March 19, 2008), at p. 19, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/31777807en.pdf (last visited May 1, 2008); "Withdrawal Assessment Report for Insulin Human Long Marvel (International Nonproprietary Name: Isophane Insulin Injection)," Procedure No. EMEA/H/C/000846 (published March 19, 2008), at p. 19, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/7034908en.pdf (last visited May 1, 2008); "Withdrawal Assessment Report for Insulin Human 30/70 Mix Marvel (International Nonproprietary Name:
Biphasic Insulin Injection)," Procedure No. EMEA/H/C/000847 (published March 19, 2008), at p. 19, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/701790en.pdf (last visited May 1, 2008).

during clinical development, *i.e.*, before the approval of Omnitrope®. During the conduct of the phase III study that was necessary to understand if the efficacy, safety and immunogenicity of Omnitrope® were similar to that of the innovator biologic (Genotropin®), 57% of the children treated with Omnitrope® developed an immune reaction (as opposed to 2% of the patients who received the innovator biologic).[130] This immune response was not predicted by analytical testing. Omnitrope®'s sponsor addressed this problem by re-developing its purification process and conducting a second clinical trial to gain approval.

It must be stressed that this immunogenicity issue was resolved before Omnitrope® was approved in any region. However, if this product had been approved without clinical data, an unknown number of children in clinical practice – rather than "just" those children in a clinical trial – would have experienced antibodies to Omnitrope®. This experience illustrates the necessity of requiring clinical trials prior to approval of biosimilars to ensure patient safety.

[130] See European Medicines Agency, "European Public Assessment Report for Omnitrope, Scientific Discussion," (April 12, 2006) at p. 24, available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en6.pdf (last visited April 18, 2008).