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May 1, 2008

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health

The Honorable Nathan Deal
Ranking Member
Subcommittee on Health

Dear Mr. Pallone and Mr. Deal:

Thank you for giving the Novartis Group of companies the opportunity to respond to your questions on the subject of Follow-on Biologics (FOBs), mailed to us by letter dated April 3, 2008. Please find our answers enclosed.

Novartis, as a global leader in both innovative and generic medicines, is uniquely positioned to contribute to the legislative dialogue on FOBs. Twenty-five percent of our innovative new therapies under development are biologics, and our Sandoz generics business has received four (4) biosimilars approvals in Europe, as well as US approval, under the existing 505(b)(2) pathway, for the first follow-on version of a recombinant biologic.

The needs of patients must be foremost in establishing a new regulatory pathway for off-patent interchangeable biologics in the US. In that regard, competition among high-quality, safe, effective medicines, including branded and follow-on versions of off-patent biologics, spurs innovation and expands access to more affordable biologics. In addition, by offering savings to government and private payors, follow-on biologics will free up health care dollars for further investment, and validate the continued and beneficial, free-market pricing of innovator biologics.

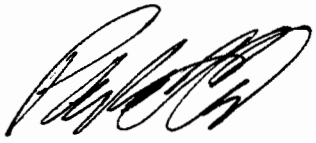
This is an exciting time for biotechnology. The industry is now past proof-of-principle, and investment dollars freed up through competition will be well spent on research and development of exciting new medicines addressing unmet medical needs. In this context, it is time to upgrade our regulatory approaches and enable FDA to approve all products based on data derived from state-of-the-art science, rather than constraining FDA's ability to evaluate medicines with unduly rigid data requirements or artificial barriers to entry codified in a statute.

As reflected in our enclosed answers, the Novartis Group of companies supports a balanced position on FOBs that enables rigorous regulatory standards to be applied consistently by the FDA to all products, including innovator and follow-on biologics; one that respects intellectual property rights; and, finally, one that provides an appropriate exclusivity period for innovator biologics.

As we and other companies have demonstrated through biosimilar approvals under the European pathway – a pathway which uses a regulatory approach based on the comparability concept initially developed by the FDA in collaboration with the pharmaceutical industry in the mid 1990's – science and technology have progressed to enable the development and manufacture of safe and effective, lower cost versions of off-patent biologics.

I hope you find our perspective useful as you endeavour to reach a consensus on legislation granting the FDA the authority to implement a FOBs pathway, fully consistent with patient safety, without unethical duplication of data or unnecessary roadblocks to approval of comparable FOBs, and providing a period of exclusivity sufficient to support robust investment in the expensive and uncertain research and development of innovator biologics.

Kind regards,



Paulo Costa
President & Chief Executive Officer

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

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

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?

   In reference to biologics, immunogenicity can be defined as the properties of a biologic that are capable of eliciting an immune response. When patients are exposed to a biologic, such as a therapeutic protein that can be seen as foreign to the body, the biologic has the capacity to be immunogenic (as occurs, for example, in organ transplantation). If a biologic is immunogenic, the most common response is the formation of antibodies, which is the measure of immunogenicity most often used during the clinical testing of innovator and follow-on biologics. Not all biologics are immunogenic, and many never elicit a measurable immune response. In the case of individual therapeutic replacement proteins, such as those represented by biologics and biotechnology-based products, the responses vary, and may be good or bad for patients. In all cases, the potential for immunogenicity is irrespective of whether the biologic is an innovator or follow-on product and reflects intrinsic properties of the biologic product itself. However, follow-ons will be able to be assessed relative to their reference, whereas a brand new product must be assessed from scratch.

   Vaccines are explicitly designed to create immune responses that cross-react with a bacterium or virus and protect the individual against that disease, whereas other biologics may represent a replacement for a deficient human protein or the delivery of a therapeutic capable of targeting or modulating a specific mechanism of disease. In the case of therapeutic biologics, an immune response is not useful, and it is less likely since the goal is to replicate the specific protein lacking. Immune responses are more common when animal sources are used (such as insulin from cows or pigs), and less common with biotech products where the goal is to mimic the human protein. In many cases, even the immune responses that do occur have no affect on clinical outcome. However, it is always important to consider immunogenicity for any biologic, acknowledge that it will depend on the type of biologic, and accept that the potential for immunogenicity applies to every biologic product, and can even vary between different batches of the same product. In addition, it is important to better use our increased and increasing understanding as to the molecular basis for immunogenicity, which include aggregation, misfolding, impurities, the presence of certain glycans, and other measurable attributes, which will form the basis of the analytical component of the comparability assessment between the follow-on biologic and its reference product. While immunogenicity varies, is not yet entirely predictable, and is potentially serious for any given patient, this risk must also be balanced with the value of the treatment/severity of the condition being treated. In all cases, the

potential for immunogenicity is irrespective of whether the biologic is an innovator or follow-on product.

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?

   It is important to monitor the use of all biologics for unwanted and potentially harmful immune responses following the initial exposure of patients to biological products, for example as part of careful post-market surveillance. However, immunogenicity testing should not be mandated by a statute for follow-on biologics, and rather should be regulated in the same manner as it is for innovator biologics, following the discretion of FDA. Such deference to FDA is appropriate because immunogenicity is a risk that applies equally to all biologics, and the innovator products are the ones that we will always know the least about at the point of initial approval. Further, to the extent that comparability has been demonstrated analytically and functionally between a follow-on biologic and its reference, the probability of a difference in immunogenicity between the final products is substantially reduced (this also applies after manufacturing changes, and in the case of Eprex where later batches induced PRCA and it was later shown that the pre- and post-products were not comparable).

   Historically, we have delegated the responsibility to the FDA to appropriately judge what is needed by way of both pre- and post- approval studies for any biologic, and this should continue to be the case for all the requirements necessary to demonstrate safety, purity and potency, including immunogenicity, at the point of initial approval and in the post market setting. If it were to be determined that, in the future, there is particular reason to focus on immunogenicity, then any such requirement would necessitate amending the existing PHS Act statute for all biologics. However, the history of the FDA oversight, in assuring the quality of the biologics marketed in the US, supports them being given the discretion to decide which studies are necessary to demonstrate safety, purity and potency on a case-by-case basis, and that Congress cannot and should not attempt to predetermine the scientific basis of these decisions. FDA has already established the concept of comparability, and led worldwide in its safe implementation, to facilitate manufacturing changes for innovator products, and these approaches have taught them, as well as sponsors, a lot about the management of risk in the context of one biologic being compared to another. These same principles, of comparing two products in head-to-head analytical, functional, and if necessary clinical assessments, can be applied to follow-on biologics. Comparability demonstrated through analytical and preclinical testing in and of itself reduces the risk of a difference in immunogenicity between two products, and the FDA should make an educated assessment when immunogenicity studies are necessary.

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

FDA has appropriately exercised its discretion regarding the need for immunogenicity testing during the course of evaluating the safety and efficacy of innovator biologics following manufacturing changes. The outstanding safety record of biologics marketed in the US, many of which have undergone multiple manufacturing changes, demonstrates that the FDA is making careful and responsible decisions. Decisions regarding the need for immunogenicity testing for manufacturing changes for either innovator or follow-on biologics should not be mandated and rather should be determined at the discretion of the FDA on a case-by-case basis. FDA has demonstrated a strong track record of evaluating analytical, preclinical, and historical data to inform the Agency's decisions, and this form of regulatory discretion with respect to immunogenicity testing should continue for all biologics.

FDA's record is particularly commendable, since to date all of the licensed products are innovator products, which by definition are the ones that we know the least about at the point of initial approval and on which only limited studies have been done at the point at which a product is first marketed. And this is particularly true for those biologics for orphan populations where only small studies are feasible.

Immunogenicity has been measured and monitored in clinical studies in many, but not all, instances of approval of innovator products, but has not proven to be the basis of many serious adverse events. Comparability studies, which include analytical and preclinical studies, are used by innovators to support manufacturing changes to their own products, and do not routinely require immunogenicity studies, and even those instances of comparability failures resulting in unacceptable immunogenicity have not been observed in the U.S. (those that are most often cited in the U.S. occurred in Europe but even then very rarely and with one particular innovator product, Eprex. In the Eprex case, analytical comparability had not been shown for what was considered a formulation change rather than a manufacturing change). In the future, and for all biologics, it is important to better use our increased, and increasing, understanding as to the molecular basis for increasing the risk of immunogenicity, which can include aggregation, misfolding, impurities, the presence of certain glycans, and other measurable attributes. These are some of the assessments which will form the basis of the analytical component of the comparability testing following innovator biologic manufacturing changes and between the follow-on biologic and its reference product.

Given that FDA has done such a commendable job with all the biologics under the Agency's existing authority, no immunogenicity testing, or any other specific testing, for any biologic needs to be mandated by statute. FDA should be given discretion regarding the need for immunogenicity testing for all biologics, and be allowed to make a case-by-case, data-driven decision on exactly what testing is needed to assure that every biologic is safe, pure, and potent (as is required in the PHS Act itself).

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 appropriate that there be scientifically-sound extrapolation between indications for those biologics where enough is known about the reference product and how it works in the body. The demonstration of comparability for one indication, including analytical, preclinical and where needed clinical studies, for a biologic with more than one indications that share mechanism-of-action will apply to all those indications, and to require repetitive studies in a statute would be inappropriate.

For biologics, to a greater extent than small molecule drugs, it is often known what the protein does in the body (the so-called mechanism of action is understood). During the earlier years of biotechnology, the goal had been to make replacement human protein for conditions where the mechanism was well understood. If the mechanism of action is known, the pertinent structures can be systematically and thoroughly investigated analytically and biologically and, if comparability can be shown, there should be no need to do repetitive clinical studies. This judgment is appropriately delegated to FDA subsequent as part of the Agency's assessment following FDA's evaluation of the comparability data. The sponsor of the innovator biologic may or may not have done extensive separate clinical studies when they sought approval for different indications sharing the same mechanism of action. However, by the time of the approval of a follow-on biologic, there will have been many years of use with the innovator product, and also additional information in the published literature and amongst the health care community. To the extent that it is clear how the biologic works and the subsequent sponsor has thoroughly characterized their product relative to the reference product using appropriate state-of-the-art analytical and functional studies to demonstrate comparability, it is appropriate to allow scientifically-sound extrapolation between indications. If different mechanisms of action apply for different indications, then appropriate functional studies for each mechanism of action may be appropriate and that possibility will need to be assessed by FDA. However, in all cases these decisions should be left to FDA's discretion, just as is presently the case for innovator products.

To require, in a statute, what may already be unnecessary and/or unethical repeat animal and human studies would be unfortunate. In all cases, just as innovator

products have to provide a complete data package to support an indication, so must sponsors for follow-on biologics, but the details in that package should not be presupposed in legislation, but left up to the implementing authorities, namely the FDA. It is appropriate that the statute define the standard to be met, and highly similar is the emerging standard for comparability worldwide, and then FDA can monitor that this standard has been achieved by any given product, innovator or follow-on, on a case-by-case basis.

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 key for any new statute enabling follow-on biologics is to impose consistent, appropriately high, science-driven and data-dependent standards for all biologics – and so, to the extent that post-market studies are required for innovator products, they should also be considered for follow-ons with the same public health goals in mind. It should be noted that standards can stand the test of time whereas the data to demonstrate that those standards have been met will change as technology progresses.

   The FDA can interpret these standards, applying state-of-the-art scientific requirements for all sponsors and the requirements can evolve for all biologics as the science progresses – for example new analytical assays should replace old ones as they become available. Likewise, there should be consistency in applying post-market expectations to all products, innovator and follow-on, and the greatest variation can be expected to be in the type of biologic and its application, not its sponsor's business model (which should be irrelevant to FDA).

   FDA's judgment and discretion, building off years of experience with innovator products, can be used to apply appropriate requirements but not to presuppose, indeed require, blind repetition if to do so would be unnecessary or require unethical studies. For some follow-ons, experience with the innovator may suggest more intensive post-marketing studies and for others less. In all cases, without exception, it will be important to keep comprehensive records of which patients have received which products, be they innovator or follow-on.

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?

The INN system, administered by WHO, with the concurrence of its 193 member countries, has worked well for over 50 years. Since its inception the system has applied globally to biologics as well as drugs, and since 1982, when the first recombinant product was approved, also to biotechnology products.

The INN indicates the active ingredient in the product, and is NOT a name for the product itself (which may come in multiple formulations and doses all of which share the same INN but are not interchangeable). Similarly, multiple innovator products have been produced by different manufacturers that share the same active ingredient, but which have never been compared in head-to-head studies and have the same INN (for example multiple epoeitins, interferons, human growth hormones, insulins). The FDA is unambiguous in its continued support of the existing system – " The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world's public health, especially in facilitating the exchange of scientific data and reports on various products with the same active ingredient(s)" (see http://www.fda.gov/cder/news/biosimilars.htm for the full statement submitted to WHO September 1, 2006. Accessed 16April08).

The INN system is voluntary and sponsors apply for an INN ahead of their regulatory submissions in the jurisdiction in which they plan to market, but the INN once issued applies worldwide. In Europe, where biosimilars are already approved and marketed, most sponsors have received approval with the same INN as their reference product and these names will now apply worldwide. In the U.S., the U.S. Adopted Name (USAN) Council within the American Medical Association usually follows the INN. Some US legislative proposals have suggested that a non-interchangeable follow-on biologic should be presumed to have a different active ingredient, hence a different INN, and yet that an interchangeable follow-on should be presumed to have the same active ingredient and hence the same INN. However, such a system would preclude a subsequent transition from biosimilar to interchangeable biosimilar as the INN does not change.

Given that this is an international system convened under WHO, it would be inappropriate and contrary to public health globally, for the U.S. to create a system on naming for follow-on biologics that is incompatible with that of the rest of the world. Further, since the existing INNs are issued based on the active ingredient, all biosimilars should have the same INN since a biosimilar cannot be approved as such if it is not comparable to its reference product. Indeed the efforts by some to prevent the use of the same INN by follow-on biologics/biosimilars could be interpreted as a thinly-veiled attempt to impede their widespread use. In the US the state laws would have to be changed to accommodate substitution for products with different INNs, even if the FDA were to have designated them as interchangeable based on their being comparable with their reference product.

This is contrary to access, competition and sound public health policy. It is much more appropriate to take the FDA assessment of comparability as evidence that the active ingredient can be given the same INN. This is a much higher standard than previously has been applied to the issuance of INNs.

US legislation to create a new regulatory pathway for the expedited review of interchangeable follow-on biologics does not need to address naming as the existing WHO system can apply to these biologics just as it has to all other pharmaceuticals for over five decades.

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?

   If the standards of comparability ("highly similar") are applied to follow-on biologics, then the subsequent product will share the same mechanism-of-action as its reference product.

   If the mechanism-of-action is unknown for the reference product, then the sponsor of the follow-on biologic may subsequently ascertain it as part of their own development package, or they may demonstrate tighter adherence to other aspects of their comparability package in order to justify their approval – including analytical, preclinical and clinical studies. If they are unable to demonstrate comparability, then approval of their product as a follow-on biologic may not be possible. It is certainly never envisaged that a follow-on biologic and its reference product would have different mechanisms-of-action.

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?

   All biologics contain variation with respect to particular attributes measured as part of the product and process development, and the ranges that are acceptable for each of these form the basis for manufacturing controls as well as release specifications for the final product. As long as follow-on biologics fall within the ranges of its reference product then they should be considered as comparable to the reference as different batches of the reference product are to each other.

   The degree of variation of innovator biologics between batches, and subsequent to manufacturing changes, will depend on a number of factors such as the sourcing (in general, naturally sourced biologics such as those derived from animal tissues, or human sources, including blood and cadavers, show the greatest variation, and biotechnology derived products the least) as well as the specifics of the products

themselves. Some are mixtures with multiple active ingredients, and others have the biological activity attributable to a specific molecule, but this molecule can vary widely in its size and complexity for different biologic products. However, if the principles of comparability are applied consistently to both the innovator product undergoing a manufacturing change, so affecting the allowable batch-to-batch variation, and to the follow-on, so affecting the between manufacturer variation, then the final products will be within the same ranges in terms of acceptable variation. For a follow-on biologic this means that the variation of any particular attribute must be within the "goal posts" of the chosen reference product. If for a given attribute, a follow-on biologic is outside the range of the sample set of the reference product, the subsequent sponsor will have to use thorough characterization to qualify that difference as not relevant to the clinical outcomes that will occur with the use of the product. Qualification will include the presentation of physicochemical, biological, preclinical, and/or clinical data as well as literature references.

And just as the innovator does not change names, or even indicate on the label that there has been a manufacturing change, and indeed is presumed to be interchangeable pre- and post- that change, there should be no issues raised for a follow-on applying these same criteria.

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?

The biologics industry has an extremely good safety record with very few serious adverse events being attributable to biotechnology-based products. Just as the PHS Act does not require, in the statute itself, that innovator biologics be subject to clinical trials, so it would be inappropriate and inconsistent to always require such trials for follow-on biologics. It will always be the truly innovative biologic that we know the least about at the point of its initial approval, and FDA has demonstrated its ability to evaluate these for safety, purity and potency for well over a century.

Market acceptance is dependent on the FDA's use of consistent and appropriate regulatory standards for all biologics, and by applying those that they currently apply to innovator products, FDA will be building on the public trust in the biotechnology industry as well as furthering confidence in the Agency. FDA should be given discretion to apply these consistent regulatory standards to all biologics, by deciding on a case-by-case basis the data necessary for any particular product to demonstrate they have reached those standards, and this is irrespective of the business model of the sponsor. This will also allow progress in the analytical sciences in particular to be captured, and state-of-the-art testing to be applied to all biologics. We should not force the FDA to impose an arbitrary requirement such as clinical studies when these are generally lower resolution

than modern analytics and more expensive even as they yield less information. Clinical studies, like all other forms of preapproval investigation are an important component for consideration in the development of follow-on biologics and the assessment of their comparability to a reference product, but they are not the best in all circumstances. Across the board, FDA should be encouraged to only require actionable data be submitted as part of applications and to enable new testing methods to replace old, and thereby facilitate the efficient and optimal development of all biologics.

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?

    There have been several cases where FDA has approved protein products under section 505 of FFDCA with either no clinical trials required or less than full clinical studies conducted. The resulting marketed products have not demonstrated any unusual or disproportionate safety issues.

    The FDA has approved a biologic drug as an ANDA without clinical studies in the case of the Menotropins (approved January 30th, 1997), although this product was never marketed. Under the ANDA requirements no clinical trials could have or were required for the original approval of the Menotropins.

    A number of follow-on versions of biologic drugs have also been approved using the 505(b)(2) NDA pathway, in which there is an innovator reference product, and for which less than full clinical studies are required. For instance, in the case of the hyaluronidases, a series of complex animal-sourced products, as well as one human recombinant product, were approved and only a single and extremely limited allergenicity study having been conducted (which is done according to the requirements of the USP Monograph and compared to, a now depleted, USP reference standard of the discontinued reference product, Wydase). None of these products were thoroughly characterized, and all of the hyaluronidases are large complex proteins (around 500 amino acids) and extensively glycosylated. There are also examples of calcitonins and glucagons, which are smaller proteins, that were approved as 505(b)(2) NDA's and for which only limited clinical studies were required.

    On May 30th, 2006, Omnitrope (somatropin) became the first and is still the only instance in the US of a follow-on biologic that is itself a recombinant product, and that references a recombinant reference product (Genotropin), and that was approved on the basis of a demonstration of comparability at the analytical, functional, as well as clinical level. It was approved as a 505(b)(2) because the reference product happened to have been approved under FFDCA as a 505(b)(1) biologic drug and so the Hatch Waxman pathways were available. In the EU, Omnitrope was the first biosimilar approved using the new pathway. In the FDA's

own words[1] "we [FDA] have determined that the active ingredients of Omnitrope and Genotropin are highly similar with regard to their physicochemical, biological, pharmacokinetic, pharmacodynamic, and clinical characteristics." (page 14); further "Sandoz has established that Omnitrope is highly similar to Genotropin without reference to proprietary CMC data in Pfizer's Genotropin NDA. Nevertheless, as Sandoz has demonstrated in its Omnitrope application, for this relatively simple recombinant protein, it is possible to determine that the end products of different manufacturing processes are highly similar, without having to compare or otherwise refer to the processes." (page 15); and "Moreover, pharmacokinetic studies conducted by Sandoz show that the half-life and clearance of Early Omnitrope, Liquid Omnitrope, and Genotropin are highly similar, which further supports Omnitrope and Genotropin's clinical comparability" (Page 36). Thus, Omnitrope, albeit for an FFDCA biologic drug but recognizing that the regulatory pathway does not change the scientific principles, shows that the concept of comparability (defined as highly similar) can and has been used by the FDA for the evaluation and comparison of two products from entirely different sponsors, and resulted in an assurance of safety and efficacy for the subsequent or follow-on biologic.

11. Omnitrope is approved in the U.S. (albeit as a 505(b)(2)) and in Europe (as the first biosimilar).

    a. Have patients experienced any problems?

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

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

    Omnitrope, a somatropin (rDNA origin) for injection recombinant, is approved for long-term treatment of pediatric patients who have growth failure and long-term replacement therapy in adults with growth hormone deficiency. In Europe Omnitrope was the first biosimilar approved using the new regulatory pathway. In the US Omnitrope was approved as another 505(b)(2) biologic drug, but the first one that is a recombinant follow-on biologic that references a recombinant innovator product, and that used comparability and quality-by-design approaches as the basis for its development, evaluation and approval. According to the FDA, Omnitrope is highly similar to Genotropin in its pharmacokinetic/ pharmacodynamic, safety and efficacy profiles, which is a very high regulatory standard and the same comparability standard currently applied to brand products when they make manufacturing changes.

[1] FDA response to the BIO, Pfizer, and Genentech Citizen Petitions (May 30, 2006), available at http://www.fda.gov/ohrms/dockets/dockets/04p0171/04p-0171-let0002.pdf (accessed Apr17, 2008).

To the best of our knowledge, the use of Omnitrope by patients in Europe matches the SmPC (Summary of Product Characteristics is the EU Label), and in the US matches the prescribing information to the same extent as all other human growth hormones. While we do not have access to the comparable information resulting from the use of Genotropin, the reference product for Omnitrope, we are unaware that the two products are showing any clinical distinctions amongst those patients that have had access to, or been treated with either or both. Pharmacovigilance for Omnitrope is being conducted in Australia, Europe and the US and being documented with utmost care. In the latest Periodic Safety Update Report to the European regulatory authorities no exceptional events were reported. The approvals in both EU and US are relatively recent (early 2006), and subsequent to the original approvals, more patient-friendly formulations have been approved as supplements, and we would anticipate that this will continue to further increase the utilization of Omnitrope.

Based on anecdotal evidence it is our understanding that patients are being switched from the reference product, Genotropin, to Omnitrope, and the product is also being used for additional indications at the physicians discretion, just as is the case for the other somatropins. In Europe, it is our understanding that such decisions are made by the health systems of the individual countries, with physicians being part of the process (such as the health authority tender in one European country recently won by Novartis, and where the patients are in the process of being switched to Omnitrope) and, in the US, by health plans in conjunction with physicians. While physicians are part of the decision making process in the US, we understand that some plans are arranging their reimbursement to encourage the use of Omnitrope (it is substantially cheaper than Genotropin based on a 35% lower list price[2]), and further that some plans are not reimbursing any other somatropin than Omnitrope. As such the cost to health plans, as well as to patients, is likely to become an increasingly important factor in the use of Omnitrope, versus its reference product Genotropin.

Novartis strongly supports a balanced position on follow-on biologics, which advocates that the same standards of high quality and science consistently be applied to all medicines, ensures respect for legitimate intellectual property, and recognizes the role that generic drugs and follow-on biologics can play in the health care system.

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

[2] Novartis Press Release, March 12, 2008, "Sandoz enhances patient access with launch of Omnitrope(TM) Pen 5 with liquid cartridge," available at http://www.novartis.com/newsroom/media-releases/en/2008/1200079.shtml (accessed April 23, 2008).

biologics approved under the FFDCA as well as those regulated under the Public Health Service Act?

There is no need to transfer those products that have historically been regulated under 505, and that were approved according to those statutory standards, as a demonstrated pathway already exists for these products.

Indeed, to approve follow-on biologics according to the PHS Act standards of safety, purity and potency when the original reference product was subject to the FFDCA safety and efficacy requirements could generate unnecessary confusion and grounds for dispute in a manner that neither enhances the quality nor expedites the availability of competing products when all patents have expired, and raises further questions as to the assignment of innovator products in the same categories (principally the hormones). Comparability is already used with both FFDCA and PHS Act products, but needs to be applied in the context of the follow-on and reference being held to the same statutory standard - unless we were proposing that all products reach the standards of both statutes, in which case they should be melded and one statute applied henceforth. Since FDA has an existing pathway for FFDCA products, has experience with it and is expressing no reservations with respect to that existing authority, it makes sense that the legislation concentrate on the one lacking authority and all that is needed which is an expedited pathway for interchangeable follow-on biologics that reference PHS Act licensed innovator products when their patents expire.

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?

Biologics in the U.S., including biotechnology products as well as all biologics subject to manufacturing changes, have an exemplary safety record in the U.S. FDA should continue to be given discretion in making data driven decisions such as determining the studies that are needed case-by-case to make a manufacturing change to an existing product, in addition to being granted the additional authority to evaluate follow-on biologics referencing a previously approved biologic using these same science-based comparability standards for all cases (the standards can be consistent while recognizing that the data will vary as the science continues to progress).

Comparability was developed by FDA along with the innovator industry in the mid 1990's (at that point no generic company was making biologics) and the concepts articulated in the resulting guidance (no statute or regulations were considered necessary) has been so successful that they have been developed into globally-applied regulatory principles (ICH Q5E). This standard subsequently became the basis for the successful European biosimilars system.

As Dr. Woodcock testified during the question and answer session at the Waxman hearing last year (26 March 2007), in the vast majority of cases of the use of comparability by sponsors to make manufacturing changes to innovator products, clinical trials have not been required by the Agency. This along with the continuing overall excellent safety record, and on-going close FDA oversight of all marketed products, confirms that the Agency's substantial history and experience can continue to be appropriately relied upon by the U.S. Congress, and that any statute enabling FOBs does not need to be "over-engineered" in terms of precise regulatory requirements, any more than the PHS Act itself is. Over a decade of substantial use of comparability protocols, and the innovator industries' continued enthusiasm for this approach, confirms industry's support for these concepts too. FDA can safely be given discretion in making data driven decisions such as this, just as they are with the innovator reference products - comparability is indeed a very high regulatory standard[3]. Further this will best enable the Agency to continue to capture the best science, as it evolves, for effective regulatory decision-making.

3. What FDA office should review FOBs?

The review divisions at the FDA that have handled innovator biologics have the appropriate and necessary expertise to review biologics, whereas the Office of Generics Drugs has experience comparing products from different sponsors. For follow-on biologics, a combination of these skills is needed, and what will be important is that the organization of the responsibility is assigned such that the Agency uses the best of both of these capabilities, and that the individuals assigned are the best equipped to immediately apply consistent regulatory standards (including particularly the PHS Act requirements) to all biologic products.

The Office of Generics Drugs has traditionally, for legitimate and obvious reasons, concentrated on small molecule drugs and FFDCA regulatory requirements, and they have very limited experience with biologics, but they do have highly pertinent experience nonetheless with the comparison of filings from multiple manufacturers and in applying consistent standards in such settings. Clinical studies are precluded in the Hatch Waxman-enabled Abbreviated New Drug Applications (ANDAs) that they review, and so OGD staff have very little experience with clinical studies. The Review Divisions represent perhaps the opposite situation. Thus in times of resource and overall budget constraints, when clinical studies are expected to be a part of an expedited BLA pathway in the

[3] Likewise, the use of comparability with innovator products has shown it is a very high standard. "It sends a very loud message and sets a very high bar," according to Alison Lawton, Genzyme's senior vice president for regulatory affairs. And she notes that Genzyme had the advantage of having full access to all the original information about the drug and still had trouble replicating the manufacturing process exactly. See http://www.boston.com/business/healthcare/articles/2008/04/22/fda_rejects_genzyme_request_for_myozyme/ (accessed April 23, 2008).

foreseeable future, and even though it is proposed that follow-on biologics be subject to user fee requirements, it makes sense to have the FDA capitalize on both sets of existing expertise and create an appropriate organization mechanism to best and fairly evaluate all biologics. The priority must to ensure that consistent and appropriately data-driven and scientifically-sound regulatory standards are applied by the FDA to follow-on biologics, and that they match those that were applied to the reference products.

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 "highly similar" standard is a well-established regulatory criterion that the FDA already routinely uses extensively with innovator products making manufacturing changes. Thus FDA can readily and immediately apply this globally-accepted standard to follow-ons that reference previously licensed PHS Act innovator biologics, just as they have already done so for the FFDCA case of Omnitrope.

   The use of the term "highly similar" in the draft legislation is derived from the definition of comparability in the ICH "Guidance for Industry Q5E Comparability of Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process" published in the Federal Register June 2005:

   > "Comparable: A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality."[4]

   Hence, the FDA is already routinely using this standard extensively with innovator products making manufacturing changes, and indeed such a result presupposes the interchangeability of the pre- and post- manufacturing change products (and there is no change in name or labeling to show that such a manufacturing change has occurred). The FDA can readily and immediately apply this standard, and the Agency's established experience with comparing two products, to the situation of an application for a follow-on biologic that references an already-licensed innovator biologic.

5. Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue

[4] See Glossary, page 13 in ICH "Guidance for Industry Q5E Comparability of Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process" http://www.fda.gov/cber/gdlns/ichcompbio.pdf (accessed 30April 08)

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?

A statute creating an expedited regulatory pathway to allow FDA's discretion to approve follow-on biologics that reference a previous FDA-approved biologic based on the established regulatory standard of "highly similar" does not need any new regulations or guidance. FDA has over a decade of experience with comparability, and the ICH Guidance Q5E was developed with the innovator industry and the regulators in Europe, US and Japan and has therefore already gone through an extensive public participatory process.

Subsequent to the innovator industry and regulator creation of the standards in ICH Q5E, the EU has revised its entire pharmaceutical law. In the process, the EC has created new regulations, and the EMEA an extensive series of Guidelines for biosimilars, both general and specific. Stakeholders, including the biopharmaceutical industry, have had an opportunity to contribute to these as well. This biosimilars pathway is now successfully in operation in Europe and a number of biosimilars, both simple and glycosylated, are now on the market in the EU, and are being safely used by physicians and patients. They demonstrate the feasibility as well as the suitability of the comparability standard for the purposes of comparison of products from different manufacturers.

Thus, the FDA is well qualified to immediately review follow-on biologics as soon as they are given the authority to do so, and as soon as sponsors are allowed to file such applications.

As with all applications, if the FDA sees common problems and the need for guidance, then it is well within the Agency's mandate to propose such guidance, often working with the industry to develop it. However, guidance reflects the current thinking of the agency, and is not a mechanism designed for the FDA to create new policy. Guidance can and should evolve as the science develops. It is also a time-consuming process, often taking many years and some guidances are never finalized. The guidance process should not be used to delay applications or approvals, especially when the result of guidance, even when final, is not binding on either the Agency or the sponsor, and the approval of each application must be evaluated on a case-by-case basis. Regulations are not needed as existing mechanisms and standards would be those already being used by the FDA.

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?

The review of each biologic application takes significant FDA resources, and while a follow-on biologic application will include a different data set from that of an innovator product, it will still need careful and thorough review. User fees consistent with those for current full BLA's should more than suffice.

The follow-on application will contain data provided by the new sponsor that they have developed on their chosen reference innovator product in head-to-head studies with their own independently developed product, and thus the follow-on sponsor's regulatory filing will include data on both products that the FDA will never have seen before. However, while complete in and of itself, it is not anticipated that a follow-on application will be as extensive as that of a full BLA since a lot will already be known from the analysis and previous use of the reference product, such as dosing. As such, the suggestion in all of the legislative drafts to date, that a standard user fee will be applied to any follow-on application (unlike a generic drug application which does not pay a user fee) should cover the incremental costs of the availability of the new regulatory pathway for interchangeable follow on biologics to PHS Act reference products.

Interchangeability[5]

1. Does current science permit an assessment of interchangeability (substitutability[6]) 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?

   There are a number of examples where complex biologic products have been judged to be interchangeable (substitutable) by sponsors, as well as

[5] **Definition of Interchangeability:** A regulatory decision made by the FDA/EMEA reviewers, and based on the data in the dossier filed by the sponsor. In the case of small molecule drugs, this is termed therapeutic equivalence, which comprises pharmaceutical equivalence (chemical identity) and bioequivalence (usually a PK/PD study in human volunteers). This is represented through the AB rating system. In the case of a follow-on biologic (FOB), the decision on interchangeability would be based on comparability and its established regulatory standard of "highly similar", at the structural, functional and clinical levels. Data established that this standard has been met would be obtained by the follow-on biologic sponsors from head-to-head studies conducted on its own follow-on biologic and on the reference product. The regulatory standard of comparability was initiated as guidance by FDA in 1996; it is now well established and in routine use by current manufacturers when making manufacturing changes to their own products (applies to biologics and drugs), and it is internationally agreed (ICH Q5E).

[6] **Definition of Substitutability**: A practice-of-medicine, practice-of pharmacy decision that is NOT the responsibility of the regulators, but that needs to be based on the regulators being the only ones to see that actual data on any medicinal product. For small molecule drugs, it is implemented through the recognition by the state Boards of Pharmacy of the appropriateness of letting the designation of therapeutic equivalence enable substitution under state law, but always allowing for the physician to make the final decision on any individual prescription. The details of the state laws vary but the principle is the same, and could likewise be applied for biologics that have been designated as interchangeable.

regulators including by the FDA (for example, including the Menotropins case of an ANDA mentioned above in question number 10 under the Science/Safety section). However, a more common and appropriate example is the concept of comparability, as used by the sponsors of innovator products when making manufacturing changes to their own products including both biologics and drugs. Theoretically any product on which it is appropriate to use comparability to support manufacturing changes could be eligible for a follow-on biologic designated as interchangeable.

The concept of comparability not only permits but presupposes, indeed requires, that the subsequent product be both interchangeable (this is a regulatory decision) and substitutable (this is a generally a term used for the practice of medicine/pharmacy decision). It is not possible to make a manufacturing change using a comparability protocol and end up with a different product that is not interchangeable – that would be a comparability failure and would not be approved by the FDA, or any other regulator. The allowable extrapolation between pre- and post- manufactured products has varied extensively and includes variations in structure that do not affect clinical outcomes through to changes in active ingredients, through to entirely changing the cell line used to make a product. A well known example of the latter was with Avonex where no pre-approval clinical data was collected on the product that was ultimately made available to patients – comparability data was allowed to provide the bridge between the product on which the clinical trials were conducted and the product subsequently marketed (which was made by a different company, in a different country and therefore facility, using a different cell line). In other words, reasonable extrapolation between data sets has been allowed by regulators and this has not resulted in problems for patients.

While there are important arguments that can be made that demonstrate comparability is dependent on the full original data set used by the original sponsor to develop the original product, that is an issue of data burden, and not inherent scientific feasibility. While it will clearly be easier to demonstrate comparability, and interchangeability, on the simpler biologics sooner than on the more complex ones, this is a continuum, and there is not an absolute limit on it being possible for any given biologic in the future. However, complex mixtures may be difficult to engineer to be indistinguishable and progress in the technology may be such that creating a new product is a more viable business model.

It should be noted, that in Europe, biosimilars are approved based on a demonstration of comparability by the subsequent sponsor between two independently developed products, but the European regulatory system does not address interchangeability and as such the products are not designated as interchangeable but nor are they designated as not interchangeable. This is a decision for each health authority and not made by the regulators even though they are using the comparability standard as the basis of their regulatory decision.

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

The FDA decides today that an innovator biologic following a manufacturing change is highly similar to the pre-manufacturing change product from the same sponsor, and that it can be used safely in the same and/or different patients. This decision is based on data and the FDA reviewers experience and judgment. Likewise, FDA can be given the discretion to make such assessments on a case-by-case and data-driven basis when comparing products from two different sponsors (albeit all the data will be that of the subsequent sponsor) and also determine whether two biologics are interchangeable. The same standards can be applied in both circumstances.

Interchangeability will necessarily be an FDA determination since it must be a data-driven decision. However, the details of the testing that will be needed will evolve as the scientific capabilities continue to evolve, and will also depend on the specific nature of the biologic in question. As such it would be inappropriate to attempt to pre-determine types of testing/data in a statute or even a regulation as this would almost inevitably trap sponsors, innovator and follow-on, in rapidly superseded methods and techniques that are not the best way to ensure that any biologic is safe, pure or potent. Just as we delegate to FDA to ensure that innovator biologics achieve the statutory criteria of the PHS Act, so we can delegate to them the responsibility to ensure that follow-on biologics meet those same statutory criteria – criteria that have not changed in over a century. If the regulatory standard is also specified, then the new statute can ensure that the follow-on, by being "highly similar" (or whatever the ultimate regulatory standard chosen in the legislation becomes) to its reference product, will also be safe, pure and potent.

It is important to be clear throughout this debate of the distinction between a regulatory standard, and the data necessary to achieve the standard. The standard can be consistent and demanded statutorily and applied to all products; the data will be specific to a given product, confidential to the sponsor, will vary case-by-case depending on the nature of the product, and the expectations of what the data can show will evolve as the science progresses and the understanding of the disease being treated evolves. These improvements in data must be encouraged by whatever statute is enacted, if we are to have the best medicines available for patients.

Given that every regulatory filing is confidential, and only FDA has access to the data (to clarify this is NOT the data of the reference product sponsor, but the comparative data assembled by the follow-on sponsor that reflects the follow-on biologic and its reference product in head-to-head studies), they and only they will ultimately be able to evaluate the submission and determine if the subsequent sponsor has substantiated that their follow-on biologic is indeed highly similar to

the reference product, and can be safely interchanged/ substituted with that reference product.

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.

   Given that every regulatory filing is confidential to the applicant, only the FDA will be in a position to evaluate the data submitted and decide whether the sponsor has substantiated their assertion that any two given products are interchangeable.

   Such is the case today for an innovator making manufacturing changes to their own product, and will likewise be the case for a follow-on biologic relative to their chosen reference product, or indeed for a follow-on making manufacturing changes subsequent to their own follow-on biologic having been licensed. The statute can set the standard of highly similar, and FDA can implement the standard, and apply it consistently to all sponsors. Such an approach will allow the actual data requirements of the Agency to evolve as the science evolves, and also allow sponsors to be creative in their proposed use of new technology, and both situations will be on a case-by-case basis while the standard itself remains consistent, transparent and fair. This will also means that all stakeholders, including patients and payors, can remain confident that state-of-the-art science and technology is being used and its development further encouraged, and that FDA is able to supersede old regulatory requirements with new ones, while still ensuring safety, purity and potency for all approved biologics. FDA may choose to issue guidance or industry propose the need for it, if it becomes apparent that there are common opportunities or problems with filings, such as has occurred for innovator products to date, but such guidance should remain just that and not be blocking on applications of any sort or preclude alternative approaches.

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?

   Just as it is with guidance for innovator products, it should be left up to the FDA to decide what guidance, if any, is appropriate for any particular group of biologics, follow-on or innovator, and on interchangeability.

   There will always be the quandary between guidance for groups of products, and the necessarily case-by-case evaluation by the FDA of a particular confidential sponsor-specific dossier. The former can never be as specific as the latter, and will therefore never be sufficient to really provide a “recipe” to make a safe, pure and potent biologic. That will always be the burden on the sponsor. As such, it would be inappropriate for a statute to attempt to determine what guidance will

and will not prove to be valuable, and it should be left to FDA, just as it is now on the Agency's guidance for innovator products, to decide what guidance will allow all sponsors to appropriately learn from the experience of others. It certainly does not make sense to repeat the many years of work that have gone into establishing the standard of comparability as "highly similar" that the regulators and industry representatives from EU, US and Japan have put into ICH Q5E, and we should also not attempt to repeat the public participatory process that Europe has undertaken to generate guidelines for biosimilars in the EU, both general and class specific, for biosimilars.

As a general principle, especially given the increasingly global nature of the biopharmaceutical industry, the extent to which globally-consistent standards can be articulated and used by all regulators when evaluating all dossiers, then the lower will be the resultant cost of drug development and the greater the access of patients. FDA guidance regarding FOB's would be useful but because guidance is not binding to the FDA or the public, and only represents the "current thinking" of the FDA on a particular topic but in general terms, guidance on FOB's (or the lack of) should not be blocking to FOB applications or determinations of interchangeability. Meanwhile, all sponsors can utilize the opportunities to meet with the FDA and discuss the specifics of their application in the confidential settings that are already available. This will provide much more useful and appropriate guidance to sponsors of follow-on biologics too.

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?

   Products that have never been compared are routinely switched in the practice of medicine today, but no FDA advice is provided to physicians and the data is not captured. A follow-on biologics that references a prior product and that is evaluated as comparable by the FDA will relate two such products and hold their interchangeability to a very high standard.

   At the end of their patent life, there is necessarily extensive experience with the reference products amongst providers and patients, as well as regulators. Likewise regulators have extensive experience with the use of comparability on these products. Hence, trust can be placed in the FDA to apply these same established regulatory standards and to make data driven decisions regarding comparability-based interchangeability for follow-on biologics if given the authority by Congress.

   FDA will also continue to work with the industry to ensure sound post market monitoring, and with health care providers to ensure comprehensive track and trace of medicines dispensed so that any problems with any medicines, innovator

or follow-on, showing reduced efficacy or safety can be identified as soon as possible. This is what they do today for innovator products and all products should be subject to the application of consistent, science-based, data-driven regulatory standards.

The risks of switching a patient from one biologic to another when they have been shown to be comparable are hypothetical and probably negligible, but absent data cannot be categorically refuted (the precautionary principle). The most commonly suggested potential risk is of immunogenicity, but to date the evidence shows that immunogenicity is related to the intrinsic properties of a single product (and always more likely with multiple administrations of that same product), and has not ever been shown to be attributable to the relationship between one therapeutic biologic product from one manufacturer with one from another. The key to the safety of follow-on biologics will always be applying the appropriately high regulatory standards that we currently apply to innovator products, and this includes careful and appropriate post-market monitoring.

In Europe, while there is no formal designation of interchangeability by the regulatory authority, and biosimilars have been available for only a short time, and there is currently no evidence of any problems for patients being switched between the biosimilar and its reference product.

There is however evidence that is pertinent to these questions, and that gives us a basis for a high level of assurance that interchangeability and switching will not be inherently problematic for follow-on biologics and their reference product. We have decades of experience with multiple independently-approved biologics that are based on the same active ingredient, that have never been compared explicitly, but, because they share indications, have been given to the same patients for many years (including, especially, those for chronic conditions). As patients change employers and health plans, the availability of medicines change, and reimbursement may incent switches (albeit with every prescription written by a physician and not pharmacist substituting). Concurrently, sponsors are making manufacturing changes to existing biologics, albeit this does not result in label changes and is not easily traced (requires lot numbers). This, collectively, has resulted in many patients being switched between biologic products, and there is very little evidence in the literature that there have been any problems and changes in clinical outcomes as a result. Since most of these products probably would not be able to achieve a designation of comparable, let alone whatever additional requirements would be required for a formal recognition of interchangeability, it can give us an informal level of confidence that patients are not going to be put at risk by the FDA designating, and health providers using, biologics interchangeably when comparability has been achieved. None of the proposals for interchangeable follow-on biologics will affect existing law enabling physicians to make individual prescribing decisions for their patients, and by which the physician can know what their patient is dispensed. In the case of biologics, many are also physician administered and this will further ensure

they know what their patient receives.Patients and providers can have equal confidence in all products approved by FDA if the same standards are applied across the board. While adverse events can never be entirely eliminated, such risks will not be an increased occurrence because of interchangeability, but represent the intrinsic risk:benefit issues in making any medicines available to patients. The medicine we know the least about at the point of initial approval will always be the most innovative, and the safest medicine will always be the one that is never approved. Neither can be the basis of sound health policy as the consequences for access and treatment would clearly be devastating.

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

   Patients, and providers, such as health plans, can have equal confidence in every approved product if the same standards are applied to all biologics. More approved products will enable more competition especially if they are designated as interchangeable. The biotech industry has a very good safety record in the U.S. Interchangeable biologics would greatly improve patient access to biologics by enabling visible head-to-head competition between providers based on price not detailing. This then allows greater access to more affordable products – a public health priority that should not be underestimated. While we have heard many assertions as to the potential for a follow-on biologic to be less safe than its reference, we have heard less of the important patient priority of access to these increasingly important, but currently often expensive biologic medicines.

   Competition in the market place when patents expire will greatly increase if biologics can be designated as interchangeable by the FDA, just as was the case with small molecule drugs after the enactment of Hatch Waxman in 1984. Such interchangeable biologics, just as was the case with generic drugs, is the best means for market forces to operate and through reducing prices and enabling multiple manufacturers when patents expire, incent further innovation for new products as well as better manufacturing science itself. As long as the same consistent high regulatory standards are applied to all biologics then the risk of all adverse events can be minimized for all products, and by incenting progress in the science can enhance therapeutic options across the breadth of the industry. Even without seeking interchangeability, and as a 505(b)(2), Omnitrope has demonstrated over a 30% reduction in price compared to its reference product.

   Health plans will be greatly helped by an FDA designation that they can immediately apply, rather than having to undertake their own independent formulary decisions and assessments. This will necessitate reasonable, science-based regulatory standards being applied by FDA that can be legitimately achieved by sponsors contacting head-to-head comparability studies with their chosen reference product. The resulting interchangeable biosimilar will create increased supply that is manufactured with more modern methodologies (and

multiple manufacturers in and of themselves provide a public health assurance against the risks of interruptions with a single manufacturer). Multiple manufacturers can be reasonably expected to lead to a concomitant reduced price per unit of product, and stimulate a reduction in the cost of goods by all sponsors – including the sponsor of the off-patent reference product. While biologics may be more difficult to make, the same consequences of competition can be anticipated for biologics as has been seen with drugs, and so also help with affordability and access. Further, such competition will free up some of the health care for further investment in the next generations of new medicines, and so be a win:win for all stakeholders.

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?

   PhRMA cites the average patent term for a product entering the US market as 11 years from the data of approval[7]. This term is an average for all drugs and biologics, and biologics can take longer to develop, and their patent estates are more complicated, but not necessarily any more secure, than those of small molecule drugs. This uncertainty, and yet the need to support the innovation enabled by the ongoing and yet increasingly unpredictable research and development programs is why exclusivity is also essential. For a company like Novartis with 24% of its new products being biologics, this balance of innovation with risk and return makes such exclusivity crucial in addition, not as an alternative to patents.

   Biologics, both those approved as drugs under the FFDCA and those that have been licensed under the PHS Act, qualify for patent term restoration of up to five years to a maximum of 14 years of post-licensure patent life, if the regulatory process took a significant length of time. Biologics licensed under the PHS Act have been granted such extensions. However, as development times continue to grow, so the proportion of the patent terms left when the FDA grants the license continues to decline despite patent term restoration. The value of exclusivity is clear to the reference product holders, but potentially it as important to follow-on sponsors in terms of the predictability that it brings in a world of complex biotech patent estates.

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?

[7] See PhRMA Industry Profile 2008, available at http://www.phrma.org/files/2008%20Profile.pdf (accessed April 16, 2008).

The 14 year patent restoration is the one provision of Hatch Waxman Act that applies to PHS Act licensed biologics, in addition to small molecule drugs and the so-called biologic drugs approved under FFDCA. As such, biologics, both those approved as drugs under the FFDCA and those that have been licensed under the PHS Act, qualify for patent term restoration of up to five years to a maximum of 14 years of post-licensure patent life, if the regulatory process took a significant length of time.

While currently not subject to head-to-head competition when their patents expire, because of the lack of an available pathway and explicit authority to the FDA to designate follow-on biologics as interchangeable, sponsors of PHS Act biologics nonetheless have applied for and received such extensions, including those granting the full five year extensions. These extensions have allowed the pertinent products to have the appropriate patents extended. These products are then protected against competition through the patented matter being unable to be commercialized by others for any purpose, and not just through the potential creation of a follow-on biologic that explicitly used them as a reference as part of a regulatory filing. The value of a patent can extend considerably beyond a single product especially for biotechnology products where it may be a methodology or technology that is patented. Without this advantage, there would be little value in getting such patent term extensions since there is effectively no competition currently occurring with the product itself when patents expire. This reasoning is why a regulatory pathway is needed by which interchangeable follow-on biologics can be licensed by the FDA as is necessary for them to reach the market and compete with the original innovator product. However, patents cannot obviate the need for exclusivity, which provides for a set period of protection from the point of approval of the potential reference product, and as such accommodates delays in the development and review of the product. Given that biologics can take even longer to develop than drugs, this can allow a development program to continue even if the patents would other make this a poor business judgment.

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?

Sponsors of biologics, as well as others such as academia, have sought and assembled extensive patent estates, and these have been used and vigorously contested in some instances in the court system. The patent system has proved invaluable to the creation and generation of worth in the biotech industry – a vigorous and risky, but also very successful sector of the US economy. The top five biotechnology products now have worldwide markets approaching $5 billion EACH. Patents will always be critically important to the biopharmaceutical industry, and court enforcement, while independent

of regulatory approval, has been effective through the first 25 years of the industry. However, patents alone may not be sufficient for biologics, because the window left post approval with clear patent protection to gain a return on investment is decreasing. Hence, the value of patents along with the complementary protection of exclusivity, which gives a date certain post approval before which competition will not occur.

Biologics, including biotechnology products, have depended on their patent estates, and their licenses to the patents of others, throughout the history of the industry. However, for the older biologics, the concept of "the product is the process" applied and was legitimate absent any ability to thoroughly characterize, and hence compare, two different biologics in side-by-side studies and demonstrate their similarity at any meaningful level (and highly similar is an extremely high standard and the current basis for comparability when a sponsor makes a manufacturing change to their own product). Thus, for these older, and necessarily naturally-sourced biologic products, the expiration of those patents that did exist did not result in competition, and thus their expiration made no difference to the market for these products. For example, many of the older vaccines and most blood products do not rely on patents for their life cycle management. However, some of these products may now be able to be thoroughly characterized (such as is necessary for their sponsor's use of comparability to upgrade manufacturing as well as for follow-on biologics).

With the creation of the biotechnology industry (first US approved product was Lilly's recombinant human insulin in 1982) the role of patents in biologics became considerably more significant. First, the approvals themselves, and then entire companies, and the very nature of the products developed, became dependent on patents, down to the very research tools used to develop them. Now, as these patents begin to expire, we first face the question of whether, and then how and on what terms, there will be market-based competition for biotechnology-derived biologic products in the US. There has already been competition for many years among non-interchangeable, independently-developed products (that do not infringe each others' patents or are the subject of patent estate cross-licenses); additionally, the work-arounds to avoid such infringement often facilitated the development of different products.

Patents are anticipated to remain critical to the biotechnology industry. While biotechnology patent estates can be more complex, the history of the industry has shown they have value, and that it continues to be important that they can be disputed in the courts without interfering with the concurrent FDA licensure process. Even those who suggest that patents are not sufficient to sustain the industry, do not suggest, when challenged, that the industry wants to forego the protection that patents offer. Indeed, exclusivity is a complementary concept; exclusivity is not a substitute for patents. However, there is no need to link patent litigation to FDA approval (as is the case for drugs under Hatch Waxman). The FDA regulatory process can continue, and at the point at which a sponsor gains a

license and is ready to launch, the sponsor can make its own business assessment as to whether it want to launch at risk. A case is also made that complex patent estates remain intrinsically uncertain and this is made more so if litigation on the innovators' patents can be initiated by the subsequent sponsor prior to any actual or even imminent commercialization of the subsequent product. Indeed, litigation enabled by the artificial act of infringement created in Hatch Waxman is resulting in earlier patent litigation, and this is a cost on the innovator industry as well as an additional uncertainty for them and their products. It is also a cost for the subsequent sponsor. This process does not presently apply for PHS Act products and need not be created for these biologics. The patent laws that apply to biotechnology products should remain the same as they do for any other industry, and generic drugs can remain the exception for linking a patent process with a regulatory process – justified by the very different state of development of the generic drug industry in 1984 compared to the biotechnology industry today. Meanwhile, there are efforts underway at FDA, such as Critical Path, that aim to reduce development times and, if successful, these may help restore some patent time to the sponsors of some products.

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?

   The fundamental rights created in the Constitution for patent holders, and with which the industry has grown and succeeded, are unaltered by the FDA being given authority to review and approve interchangeable follow-on biologics. **Legislation to create a new regulatory pathway can simply give the FDA a clear mandate that will allow the Agency to manage an expedited regulatory review and approval process that will enable competing products to reach the US healthcare market. There is no need to couple these regulatory procedures to any of the Title 35 patent rights – these rights will remain unaffected by follow-on biologics and be up to the courts to reconcile as needed.**

   When any biologic is approved, as a follow-on or as an innovator product, and then marketed, any patent holder whether the sponsor of the reference product or a third party can decide whether or not they believe that their patent is infringed. If so they can sue. In the setting of follow-ons, this would be exactly the same situation as presently applies to any current sponsor or any third party that can choose to sue, or not, anyone they believe has infringed their patent, including another sponsor of any innovator biologic product. Today, no innovator sponsor receives any notification of a regulatory filing or approval of a subsequent product that may infringe any of the patents on their product. This model is also that which applies to every other industry in the US. It is the appropriate model to apply to biotechnology where it may be impossible to be certain exactly which patents are held by whom and apply to which product, and indeed the patents need not be litigated until there is a commercial product that would violate a

patent right. One proposal that may be useful for all stakeholders as part of the new pathway is if, immediately subsequent to the FDA issuing the license for a follow-on biologic, the reference product holder is given notice of say 45 or 90 days in which to initiate suit if they believe they have patents infringed; during this window, the follow-on sponsor will not launch their product. This process will allow the reference product holder to protect its rights, but meanwhile give the sponsor of the follow-on biologic an asset that has value, and this will include the possibility to launch at risk in the absence of a preliminary injunction if the follow-on sponsor is confident that it has not infringed. To enable follow-on sponsors to make this purely business decision is sound public policy.

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?

Including patent provisions in a statute creating a pathway to enable FDA to designate a follow-on biologic as interchangeable with an existing product would be a distraction and encumber the FDA with obligations beyond the Agency's area of expertise at a time when FDA already is resource-constrained. It is far preferable to leave the regulatory process to be implemented by FDA, and the patent system that already successfully protects all patents holders, including those with biotech patents, in the hands of the courts. Such a "decoupled system" will not encumber the pathway or the FDA or get in the way of immediate implementation of a regulatory pathway due to the need for special regulations.

The first patent challenge with biotechnology-based products is the one that is already faced by innovators today, and that is identifying all the patents that may apply to their product. This challenge is compounded for follow-on biologics, except that patents do ultimately expire and, at some period after the initial approval of the product, there will be a reasonable expectation that the patents will have expired. However, it is not clear that it will ever be possible to comprehensively identify all the patents that will be potentially infringed by any given product ahead of its approval and commercialization. However, since most candidate products never make it successfully through development, FDA review and approval, and marketing, it is premature to try to establish potential for patent infringement ahead of a sponsor's ability and decision to market. With no commercialization, there is no need for litigation. However, a suitable exclusivity period that runs from the date of approval will help ameliorate the uncertainties created by complex patent estates and enable development of products and uses for which the lack of patent certainty by the patent holders would otherwise mean does not occur.

The exception created by Hatch Waxman to allow patent litigation to start prior to commercialization was an exception created to support the nascent generic drug industry in the early 1980's and accede to their need for some level of patent certainty prior to launch – the argument being that generic drug companies were

not strong enough to launch-at-risk. This reasoning does not apply today to most sponsors of follow-on biologics, and it is preferable to not encumber the legislation, nor ultimately the FDA, with a cumbersome Hatch-Waxman-like patent scheme that will be inherently impossible to implement because there is no known set of patents for any given reference product and so there can be no certainty that they have all been litigated when the subsequent manufacturer is ready to launch. This scheme is quite apart from some of the suggestions that a subsequent sponsor share its dossier ahead of licensure with their greatest competitor, the reference product sponsor, in order to see that they have not infringed any of their patents.

If impractical, cumbersome or simply unusable patent provisions are created, they will preclude the use of the new regulatory pathway and so destroy the opportunity for competitive products to reach the market that have an FDA evaluation of comparability as part of their label. The European system does not attempt to link patent provisions, and allows patentees to enforce their rights independently in the courts just as is the case for every other industry.

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?

   The patent listing provisions of Hatch Waxman, while well-intentioned, are cumbersome, a significant administrative burden on the FDA, and subject to intense strategic use by both innovators and generic drug sponsors. Given that it is generally assumed that the patent estates for biologics are more complicated than those for small molecule drugs, it is impractical to try to recreate such a system for biologics. Given that it is unnecessary to link patents and FDA evaluations, and that this has never been the case through the history of the biotechnology industry, there is no point in doing so now. Regulatory approval should continue to be decoupled from patent litigation.

   The bills drafted so far to enable biosimilars have demonstrated the impossibility of creating simple and clear patent provisions that will provide any assurance to patent holders that FDA can facilitate the notification and protection of their patents. While the proposals create opportunities to begin litigation early as is presumed to be helpful to generic companies, a statute cannot create a mechanism that will provide any assurance that patent disputes will be resolved early. Further no statute can protect a patent holders right's and entirely prevent the risk of additional patents appearing at the last minute that delay launch and precipitate a further round of litigation.

   Patent litigation ends up being a significant "tax" on both sides of the industry, and if it blocks or delays products being approved and the ability to launch at risk,

then it can delay competing products becoming available, irrespective of the final outcome of the litigation. Further, any FDA obligations created under the new pathway for follow-on biologics that must be implemented by the FDA will necessarily consume Agency resources that could be better spent in areas where FDA has the expertise. It would be much wiser to leave patent rights to be covered by Title 35 and the courts just as occurs for every other industry, except for generic drugs, and "decouple" any patent issues from the regulatory process. No patent rights are lost this way, and the FDA can concentrate on the job it is best qualified to do – which is to review and evaluate biologics according to scientific and technical standards. An exclusivity provision that precludes the approval by the FDA of follow-on biologics for a set period from the initial approval of the reference product is much less burdensome. Indeed, such a provision would create zero extra responsibilities for the FDA since the notification of the approval to the reference product holder would be by the sponsor of the follow-on biologic upon receipt of the follow-on approval. The follow-on sponsor would be precluded from launch for a set period, 45 or 90 days has been suggested as appropriate, during which the reference product sponsor could choose to litigate. Given that the issuance of the approval is public, it also serves as notice to any third party patent holders who believe their patents may be infringed by the follow-on sponsor (although, in most instances, these would have also been infringed by and/or licensed to the reference product holder).

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?

   A credible case can be made that complex patent estates will always be intrinsically uncertain and expensive to defend, whereas exclusivity, which provides a period of certainty against use of the innovator product as a reference by a follow-on biologic from the date of approval of the reference product, complements patents and increases the probability of further and sustained innovation. Patents and exclusivity are different and both are valuable as a stimuli to further investment and hence further innovation. While the periods of patent protection and exclusivity will overlap significantly, the assurance that they provide to the sponsors of innovator products are different and both are necessary.

   Patents are one form of intellectual property protection, but given the complexities involved in the development of biologics and the increasing time that it takes, as well as the further delays that FDA review and licensure can add before a product can be marketed, a substantial amount of the patent term for a biologic can be consumed by the time that a biologic even begins to make a return

on the investment. In Hatch Waxman, to incent the necessary research and development of additional indications, all drugs were given five years of so-called data exclusivity, during which the FDA could not approve a product that referred to the innovator product (the "prior finding of safety and efficacy"). This only applies to FFDCA approved products and not to those products licensed under the PHS Act. In Europe, the new pharmaceuticals legislation created in 2003 precludes the filing of any generic or biosimilar for 8 years, the approval of any such product for 10 years, and a further one year of exclusivity for an additional clinically-significant indication (the so-called 8+2+1 system). The system applies to all drugs and biologics.

The European proposal is a useful concept and experience to consider for the US, but other differences in the health care systems of the two regions mean that the length of time for exclusivity for biologics in the US must be carefully considered in a US specific context. Given the investments necessary in developing innovator biologics, a minimum of 12 years of exclusivity is essential and there may be sound arguments for more. The balance that must be achieved is certainty that the period of time on the market for any product to gain a return on the investment will be sufficient to maintain investment and meanwhile that subsequent sponsors can reasonably anticipate when they will be able to offer competing products to consumers.

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?

Exclusivity can assist in sustaining innovation in future biologic medicines. While not an alternative to patents, it creates a fixed period of certainty against a follow-on referencing the innovator product, and thereby helps minimizing patent litigation, and the associated risk and costs, for both innovator and generic companies. A significant exclusivity period will allow for a number of patents to have expired such that litigation on them no longer has value to a subsequent sponsor. The availability of a new pathway would end the current indefinite exclusivity presently occurring for biologic products against head-to-head competition and a minimum of 12 years exclusivity will be an important way of minimizing disruption to the on-going development of the increasingly significant part of the pharmaceutical pipeline that is now biotech.

While discovery and development of the next generation of innovator products is essential to the existence of both the innovator and follow-on/generic biopharmaceutical industry, the cost/uncertainty element of patent disputes should not be underestimated, and hence there is additional value of defined exclusivity in reducing this cost to the overall healthcare system. This can be considered in terms of both the greater availability of the competing products, but also in the cost to get either innovator or generic product to market, and defend its place once

there into to get a return on investment. The question addresses the research and development of innovator biologics, but not that of generics, nor the cost of either at the point they reach the market place, and these are important. Also, avoiding disruption to on-going investment is an important consideration, especially as the small molecule pipelines are losing productivity, and more companies are increasingly dedicating a significant proportion of their research and development dollars to the scientifically almost limitless prospects for biotechnology. The first generation of biotech products were largely replacements for missing human proteins and we are just beginning to see the truly new, never-found-in-nature, molecules becoming available. This gives the opportunity for addressing unmet medical needs in a way never done before but it will take massive investment and that needs confidence in a time of exclusivity once on the market on which to get a return.

In terms of assessments, it is very difficult to obtain data that is meaningful but the Wall Street reaction to the Senate H.E.L.P Bill, which was expected to proceed at that time to enactment as part of the reauthorization of PDUFA, with its 12 years of exclusivity, was sufficiently favorable that investment in the biotech industry was not reduced. This suggests that that bill was not interpreted as being contrary to the innovator industry. The Senate H.E.L.P. contained a flat 12 years of exclusivity for the innovator product, during which the FDA could not approve a follow-on biologic that used it as a reference.

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

Legislation need not get into the details on improvements on existing products and their value. If the "highly similar" standard is used to compare the follow-on biologics with the reference product, then any "modified" products will be prohibited from using the new pathway. As such they will represent a full standard application after a full development program, and should qualify for whatever standard exclusivity period such an application is determined to warrant. Modified-products will be new products in the regulatory context and will be evaluated as such by the FDA, just as is the case today.

The new pathway will not apply to any products that are "modified" and their sponsors will be required to file full BLAs. Thus they should qualify for whatever period of exclusivity is awarded to the sponsors of complete BLAs as they will have the same development risk. Once a full research and development dossier is compiled, reviewed and licensed, these iteratively improved products will then have to be detailed and compete in the market place just like any other new product, and if they do not offer a significant improvement on the previously approved product they will have to compete directly with it, and any follow-on biologics that reference the original (once patents and exclusivities have expired). As long as it is possible for a subsequent sponsor to reference the first generation innovator product using the new pathway, then the presence of a second

generation product developed independently cannot undermine the competition that ensures – indeed it can only add additional therapeutic options for patients and providers.

To try to predetermine the level of innovation that will qualify for exclusivity is impossible – that is best left to market forces, which will be created by patients and health care providers based on how they value a given medicine, just as occurs today for small molecule drugs. And it may take time to evolve as experience with eth product is gained. If a full BLA (PHS Act 353(a)) gets a set period, then sponsors can decide the degree of regulatory burden they are willing to take on to achieve that initial license and what degree of incremental improvement they will believe provides the value to gain the return.

If, as is occurring in some of the legislative drafts, the burden for a follow-on biologic to get regulatory approval is greater than that for an innovator product, then the new pathway will not be used by any sponsors. The key is to balance the legitimate extrapolation between products based on data, an expedited pathway that allows the prior approval of the reference to be included, and giving the FDA the authority to designate the two products as interchangeable in exchange for a set period of exclusivity for the reference product prior to that subsequent approval. It may also be appropriate to consider a period of exclusivity for the first interchangeable follow-on biologic itself.

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

While multiple forms of protection exist, exclusivity is conceptually very different from patent protection and as proposed in the context of medicines has been applied to the medicines itself, and counted from the point of initial FDA approval. Thus the variation in the development time and any delays in FDA approval do not undermine the ultimate value of exclusivity whereas they directly erode the period of patent protection.

As proposed in the context of follow-on biologics, to be useful to innovators and provide certainty to both innovator and follow-on biopharmaceutical companies, exclusivity must protect the innovator product from being used as a reference by a subsequent sponsor of a follow-on biologic for a set period, and we advocate a minimum of 12 years, and this is best achieved by precluding the FDA from issuing a license for the follow-on until that period has elapsed.

Patents are another and very distinct form of intellectual property protection, but because they are counted 20 years from the date that the patent is filed a substantial portion of this period can get consumed before a product is ever marketed. The time can get consumed during the development of the biologic, as well as by the time needed for FDA review, such that too little is left by the time the product reaches market for its sponsor to get a return on investment. Hatch

Waxman provided up to five years of patent term restoration (up to a maximum of 14 years post approval) for both FFDCA and PHS Act products. Also to incent the necessary research and development of additional indications, even for totally off-patent products, all drugs were given five years of so-called data exclusivity, during which the FDA could not approve a product that referred to the innovator product.

A credible case can be made that complex patent estates remain intrinsically uncertain, and potentially expensive to protect, because a patent must always be defended by its holder against a challenge, or an infringement by someone commercializing a subsequent product. Hence, even should a biologic be marketed with significant patent time left, a subsequent sponsor could currently market an independently developed product that infringes and erode the market while patent litigation ensues, and the patent holder would have to initiate that litigation as the point of the subsequent products approval.

And even were a new pathway to be created that provided for exclusivity, patents will have value to their holders, even as they have limitations. Exclusivity in the context of follow-on biologics would not protect against a subsequent sponsor choosing to file a full BLA even if the product is closely related, and even if it was potentially interchangeable. Patents will remain essential to the innovator industry.

Exclusivity and patents are complementary in ensuring the health of the biopharma industry and together increase the probability of further and sustained innovation.

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

Biologics are generally complex and take considerable effort and time to develop. Small molecule drugs are trending to greater development costs too but historically have generally been less expensive to develop and manufacture, and are not subject to the same degree of regulatory challenges with respect to, for instance, getting extra dedicated capacity on line, and they generally have more options by way of raw material supplies. None the less many of the same considerations apply to both drugs and biologics, and in Europe the exclusivity periods apply equally to both.

Also the economic environment and state of the biopharmaceutical industry generally is very different from 1984 when the exclusivity period for drugs was chosen, and indeed it may be fair to revisit the data exclusivity period for drugs subsequent to the enactment of the legislation to create an expedited pathway for follow-on biologics that reference PHS Act-licensed innovator biologics.

The patent estates between drugs and biologics are different, with the latter having more extensive but still uncertain protection, especially in the context of the anticipated vigor and focus of competition by sponsors of follow-on biologics. The sponsors of follow-on biologics likely will include the breadth of the global biopharmaceutical industry in a manner that was not contemplatable in 1984 for drugs.

The Europeans have standardized their pharmaceutical law around exclusivity of eight years against filing, an additional two years against approval with an additional one year for a new indication (called 8+2+1 as shorthand) for all medicines. Given the increasingly global nature of the biopharmaceutical industry, and patient need and consumption of all medicines being now part of a global market, it is appropriate to consider the European model as a starting point for the US legislation. However, the difference in the health care and reimbursement systems of the two regions are also important to consider.

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

   Patents reward innovation, and truly innovative biologic medicines could therefore be presumed to qualify for the most extensive and appropriate patent estates.

   However, medicines, both drugs and biologics, are unique in the long time and high investments required to develop them and the regulatory regimes that they face that preclude market entry. Hence, the effective patent term that biotechnology products receive in terms of the time on the market that their sponsor can achieve a return on their investment is nowhere near the 20 year term of the patent itself. While biologics, like drugs, even when licensed under the PHS Act do qualify for up to five years of patent term restoration, up to a maximum of 14 years effective patent life, this may still prove insufficient for those molecules that have proven particularly difficult to develop.

   Exclusivity can also offer opportunities for improved applications for medicines for which all patent terms have expired - the studies to achieve these indications and their approval are nonetheless expensive and valuable public health priorities.

   Exclusivity and patents are complementary in ensuring the health of the biopharmaceutical industry and together increase the probability of further and sustained innovation on behalf of patients and health care systems.

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 are immensely valuable to innovator biopharmaceutical companies, but they do not create market certainty in a difficult development and regulatory environment. As such it would be expected that those molecules and processes on which little or no patent protection was available would become lower priorities for further development. This would include reducing the study of new indications, and in new populations. By forcing biopharma companies to make their investment choices based on the strength of their patent estate, rather than on the scientific-opportunities and the potential value of the medicine to individual patients, and the public health more generally, important opportunities will be lost. This risk can be ameliorated by creating a reasonable exclusivity period for all full applications for PHS Act products from their time of initial licensure by the FDA.

Exclusivity and patents are complementary in ensuring the health of the biopharmaceutical industry and together increase the probability of further and sustained innovation. This innovation will include contributions by American Universities and others.

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.

   There have been a series of recent studies that estimate savings from follow-on biologics to be billions of dollars over 10 years (PCMA, Express Scripts, Avalere, Insmed in order of publication), and while all make different assumptions and attribute the savings to different groups of medicines, and to different populations within the US, there is no question that the estimates are significant numbers and that there will be savings with follow-on biologics.

   Indeed according to the most recent assessment on economic savings with follow-on biologics published by Insmed, which assumes that a follow-on biologic pathway is approved in 2008 and those products already off patent could be approved by 2010, there would be a price discount of 25-35% over a 10 and 20 yr period. They calculate savings between $67 billion to $108 billion over the first 10 years, and $236 billion to $378 billion over 20 years.

   These savings can become available virtually immediately if Congress gives FDA the authority to evaluate such products, given that, as Dr. Woodcock testified at Congressman Waxman's hearing in March 2007, the Agency is already having

discussions with sponsors as to what will be needed as part of regulatory filings (assuming existing regulatory criteria and standards will be applied). However, this will only occur if FDA is given the authority to evaluate products according to a new pathway immediately and the legislation does not include any blocking requirements such as for regulations or guidance, and is overall feasible (for example absent patent provisions that require a subsequent sponsors most confidential trade secret information – their regulatory dossier - to be handed over to their principal competitor – the reference product sponsor). A simple designation of authority to the FDA to apply existing regulatory standards to follow-on biologics and to be able to recognize such products as interchangeable with their reference product would lead to the only limit being the review clock by which the FDA is bound to review user fee applications (assuming, as has been the case in all the legislation introduced to date, that user fees will be paid by the sponsors of these products).

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? Check with company.

   Not applicable

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

   It can reasonably be expected, especially in the US, that head-to-head competition by follow-on biologics will incentivize further innovation by the innovator biotechnology companies who will need to replace the products subject to competition in their portfolios. This occurs with small molecule drugs today. The lower prices of the follow-on biologics will free up health care dollars for this further investment, so the availability of the new pathway can be expected to also stimulate US economic competitiveness just as occurred in 1984 with the enactment of Hatch Waxman.

   Enabling FDA discretion will also free up existing manufacturers to upgrade their manufacturing processes, as well as the product portfolio itself, and these could lead to a reduction in cost of goods that will further free up healthcare dollars and/or enable broader access and thus confidence and commitment to the biotechnology industry.

   Legislation giving the authority to the FDA to implement an expedited regulatory pathway for follow-on biologics does not in and of itself affect intellectual property rights - patent rights will still be constitutionally protected and subjected to Title 35. To the extent the statute grants exclusivity to innovator biologics such

that they are protected from being used as a reference product by a follow-on biologic for a set period after that products initial FDA licensure, the statute would add to the protection of innovator products but only through to a certain date post initial approval of the reference product.

The US already represents the largest single pharmaceutical market worldwide, and the one for which free-market, value-based pricing is the most prevalent. Over a third of the innovator medicines in development are biotechnology-based, and there is already intense attention on the potential US biologics market with or without a new regulatory pathway for interchangeable follow on biologics, not least because the patents on the original innovator biotech products are conspicuously expiring and the top five biotech products are approaching markets of $5 billion dollars EACH. A new regulatory authority to the FDA will simply facilitate innovation by innovator companies, the production of follow-ons by any biopharmaceutical company, and the therapeutic options for patients and their providers, and assess through greater price competition in the market place. All will be valuable stimuli for the US economy. Currently the US is paying the highest prices and losing leadership in terms of these important products.

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?

   To the extent that the statute grants exclusivity to innovator biologics such that they are protected from being used as a reference product by a follow-on biologic for a set period after that products initial FDA licensure, the statute would add to the protection of innovator products. This will enhance the investment in these innovator products due to the investment value of that greater market certainty, and so help the upward cycle of enhanced biotechnology innovation.

   The biotechnology industry has begun by replacing previously naturally-sourced products (from animals and people), and shown that it can do so reliably and consistently, and is just beginning to create the truly innovative, never-found-in-nature products. As such it is only at the beginning of what it can offer patients around the world, but this dream cannot be achieved without substantial investment, especially if the excellent safety record of the biotechnology industry is to be maintained.

   Patents are immensely important but exclusivity helps minimize the “tax” on both the innovator and follow-on industry that is represented by patent litigation – a cumbersome, slow and expensive process in which even the winners pay a high price.

   Legislation giving the authority to the FDA to implement an expedited regulatory pathway for follow-on biologics does not in and of itself affect intellectual property rights one way or the other - patent rights will still be constitutionally

protected and subjected to Title 35. Indeed, the discussion about the new pathway for follow-on biologics was precipitated by the increasing awareness of the lack of competition when the patents on the original innovator products expired. It was realized by policy makers and payors, public and private, as well as by patients and the biopharmaceutical industry that there was no mechanism by which FDA had the explicit authority to license subsequent follow-on biologic products that could compete head-to-head in the market place with those on which the patents had expired. As such the present system in some way represents infinite patent life, but that is only in terms of sponsors needing a designation of interchangeability by the FDA. In terms of making new and improved biologics working around patents remains one of the drivers for innovation. This is a legitimate and intrinsic premise of the patent system that will remain unchanged by a new pathway. Hence, the opportunity for a win:win whereby more affordable follow-on biologics free up health care dollars for investment in new products, that in turn provide greater options for the treatment of unmet medical needs, just as occurs today with small molecule drugs. Exclusivity will be an important complementary component that further fosters the upward spiral of innovation envisaged by the patent system and enable more therapeutic options for all providers and patients.

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

   The current patent system has encouraged innovation in the biotechnology industry and sustained it since its inception. There are no proposals that will negatively impact the patent rights of those involved in biotechnology. However, appropriate exclusivity that gives predictability to the period on the market over which an innovator biologics can gain a return on investment could substantially increase the confidence of those investing in the biotechnology industry and so enable its considerable potential to be realized more quickly [see above for discussions on the value of exclusivity].

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.? Do we endorse the EU method of product-specific guidances?

   The European biosimilars pathway is based on the established comparability standard in which their regulators, and FDA, have extensive experience. The European process included the development of certain general and product class specific guidelines but this process and these guidelines were not blocking on applications or approvals while they were being developed. Applications and approvals continued concurrently, and indeed the applications contributed to the contents of the guidelines themselves in a constructive and iterative process.

   The guidelines that were developed are based on the same regulatory principles of comparability that were originated by the FDA during the 1990s (published as guidance in 1996), and that have achieved elaboration and endorsement through the ICH process of which the US is part (represented by FDA and PhRMA), and as such the principles that the European guidelines articulate are entirely compatible with the regulatory concepts already in use here in the US. Further, the EU guidelines solicited and received input in a public participatory process from all stakeholders, including the innovator industry and others based in the US, and while they have taken some years to complete, they form an important part of the emerging consensus as to the appropriate regulatory standards for a number of important classes of biologics and can now be expected to be the accepted standard for those medicines worldwide. Biosimilar applications were being reviewed and approved by EU regulators concurrent with the development of the guidelines, and the sponsors of these products were also constructively engaged with the regulators in the development of the guidelines using their own unique experiences to make those guidances more valuable to other potential sponsors. Indeed product specific guidance was never a pre-requisite of application or approval, and nor will it be in the future. Further, the regulators provided and provide scientific advice to all sponsors upon request in a manner similar to that available in the US.

   There is no value, given the extensive cost and effort already undertaken, in the US repeating the entirety of this process, but procedurally the US guidance procedures and formats are slightly different. It could be more valuable, if it were to be considered necessary, for the EU Guidelines on biosimilars to be integrated into the on-going ICH Guidance process and become common documents to EU, US and Japan just as is the case for other ICH leadership initiatives, such as ICH Q5E Guidance for Industry

"Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process". That would avoid each countries regulators developing guidance that then need to be reconciled to get the globally-applicable common approach that is so valuable to industry being more efficient in their product development. ICH documents are often adopted by the rest of the world and so serve the global consistency objectives of both regulators and industry. Meanwhile the FDA can use an authority delegated to it by Congress to review and license follow-on biologics that refer to a previously approved reference biologic product and, if the appropriate data is provided by the sponsor, designate it as interchangeable. This can all be achieved using the existing comparability standard that the FDA has experience with, and without delaying the availability in the US of the products that are already available in Europe.

As Dr. Woodcock testified last year (Waxman Hearing, 26Mar07), the FDA also has experience with using these approaches under the Agency's existing authorities with FFDCA regulated products, indeed has compared products from different manufacturers using these approaches, and would be simply applying the same standards and procedures to those products that are licensed under the PHS Act. Should FDA, based on the applications and emerging experience with follow-on biologics in the US, decide that further guidance to industry would be useful, they can propose it just as they do for any other topic that applies to innovator products.

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?

   There is value in global consistency, but to the extent that the US represents a very different health care model, it perhaps is better to consider the European approach as a good place to start with respect to considerations for exclusivity rather than necessarily the place to end up.

   The EU represents a group of 27 countries that have certain procedural issues that are very similar to those in the US, such as centralized review of medicines prior to their being marketed (although national reviews and mutual recognition are also possible for some products). This procedure includes the review of all biotechnology products including biosimilars. Europe all has a mixture of reimbursement systems that, subsequent to regulatory marketing authorization, also affect how quickly products are made available to patients, who gets access to the medicines and how much the biopharmaceutical manufactures are paid for the products.

   In Europe's recent revision of its pharmaceutical law, the European Community created a common exclusivity period that applies to all medicines, both drugs and

biologics. This prohibits the filing of a subsequent product for eight years from the data of the reference product's approval, a further two years against approval, and with the potential for an extra year of exclusivity, creating the so-called 8+2+1. In the US we already have the 5 year exclusivity for small molecule drugs created in Hatch Waxman (4+1, namely a four year prohibition on filing and a further years prohibition against approval of the generic drug), and the debate is now over what should be statutorily applied for biologics. The experience in Europe with biosimilars, and the already long history with biologics in the US means that an exclusivity period of at least 11 years would enable a very significant number of biologics available to be used as reference products by subsequent sponsors, while still allowing more recently approved products to be confident of a significant time on the market without competition during which they can obtain a return on their prior investment. There is also value to the same exclusivity period applying to drugs and biologics, and perhaps the 5 years for small molecule drugs in the US is insufficient. There is value in global consistency, but to the extent that the US represents a very different health care model, it perhaps is better to consider the European approach as a good place to start with respect to exclusivity rather than necessarily the place to end up, which should be a minimum of 12 years.

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?

   Products are increasingly developed for a global marketplace. However, already the availability of the biosimilars pathway in the EU is leading to those products being reviewed and approved, and so becoming available to the European patients first. This is resulting in reductions in prices and greater access to important off-patent medicines that cannot presently occur in the US unless sponsors are prepared to invest in and undertake a complete biologics development plan and file a full BLA. However, continued innovation is essential to replace the portfolios that will be subject to competition when patents and exclusivity expire, and so as soon as pathway enabling competition is available it remains essential that innovator companies are able to invest in that next generation of products – this is where exclusivity will help provide the incentives. If Europe has such incentives and the US does not, then that will affect where products are first marketed.

   Meanwhile, Canada has issued guidance along the lines of the EU approaches, and Japan is expressing similar interest. The US remains the biggest pharmaceutical market, but absent the authority to approve interchangeable follow-on biologics that reference existing PHS Act licensed products and that can therefore compete in the healthcare market directly it can be projected that two things will happen.

Firstly, and perhaps most dangerously for patients, de facto substitution will occur as health plans and payors construct formularies, that already do not include every medicine, and patients increasingly get switched between products that have never been compared for reasons of cost. Essentially, the FDA is taken out of the equation, and even though they are the only body that can access and evaluate comparative data they precluded from using this ability or to relay the conclusions of such comparisons to the health care providers who must therefore function absent this knowledge. This may make all products in a class essentially interchangeable in the practice of medicine, but will not be a data driven process, and it will not be in the interests of patient safety and good public health policy.

Secondly, the price competition in the market are less because of the reduced incentives to even make even a potentially interchangeable follow-on biologic, and the concentration of the industry continues to be on iterative improvements that require detailing and, because they required full regulatory dossiers, must be premium priced. This will mean that the US continues to pay the highest prices in the world and concurrently that patients are denied access to what may be the best medicine for them sue to affordability.

Also, such a world of limited regulatory pathways and FDA discretion dis-incentivizes the equally important innovation represented by manufacturing improvements that can enhance the quality of biotech products while ultimately reducing the cost of goods. The undermining of comparability as a standard, if the US fails to endorse it for follow-on biologics.

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?

While EMEA and FDA regulatory approval is necessary, in Europe and the US respectively, it is not sufficient alone to enable access and availability of biologics, and ultimately the payor and reimbursement systems are critical. Here the differences between the US and many of the individual European countries are much more apparent. Hence, it is appropriate to standardize the regulatory requirements to the greatest extent possible, but other aspects must then also be considered.

The laws in each jurisdiction, Europe and US, enable the regulators to implement evaluations of candidate products for subsequent market entry – the obligation always being up to the sponsor to demonstrate with data that their biologic product is safe, pure and potent. However, in addition to the regulatory requirements, overseen by EMEA in Europe and FDA in the US, there are various healthcare system elements unique to each jurisdiction that also determine the

availability of medicines to patients. However, it is equally certain, that without the availability of an expedited regulatory pathway to enable the licensure of interchangeable follow-on biologics, no health care system, public or private of whatever configuration, can purchase them and make them available to patients.

To the extent that the regulatory systems can evaluate all biologics, irrespective of sponsor, using the same parameters and applying the same standards, they can aid in the more efficient manufacture of these products by an increasingly global biopharmaceutical industry for an increasingly global patient population. Comparability is the concept being used in Europe for biosimilars, and this uses the standard of "highly similar". Since both the concept and the standard are already in use in the US, for manufacturing changes to existing biologics by their own sponsors, the extrapolation to follow-on biologics in the US too is logical.

Further, with the European system is already in place, the regulations and guidelines written, and the products approved and being marketed it makes sense to assess these for their immediate applicability here, no delays being necessary (indeed in one instance the same product is approved in the US already, just not called a biosimilar, namely Omnitrope). Since the standard is already in use in the US for manufacturing changes for innovator products, has effectively been used by the FDA for the evaluation of FFDCA products, including specifically comparing products from different manufacturers, and is a standard that FDA has testified to as being one that they have experience with and are comfortable applying, it makes eminently good sense for the FDA to be given the discretion to apply it as part of the expedited pathway being created by Congress for follow-on biologics to PHS Act reference products in the future.

It should be noted that while the European pathway is silent on interchangeability/ substitutability (it neither says biosimilars are or are not interchangeable/ substitutability), the standard that is being used is the one that presupposes interchangeability for a sponsor making a manufacturing change to their own product, and it can be applied by the FDA for interchangeable follow-on biologics here equally safely. As such, a conclusion of interchangeability for a biosimilar through its sponsor having demonstrated it is highly similar with its reference product is scientifically justified, but may not yet be acceptable for other reasons, such as reimbursement jurisdictions and policies, in any given European country. However, health care providers will be able to safely use the products interchangeably with the reference product, to the extent their local laws allow (one form of substitution albeit not the automatics substitution that will ultimately have the greatest impact through head-to-head price competition). As health care costs continue to increase, and patient access becomes ever more important to health care systems, and yet more challenging for a greater and greater proportion of the prescription drugs portfolio, this situation may lead to a more formal mechanism for interchangeability/substitution in Europe.

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? Have there been any safety/efficacy problems here or in EU? If not, can we just say they have a good safety record and the risk of a safety/efficacy problem is irrespective of whether it's a brand or follow-on product?

   There have been no safety problems attributed to biosimilars in Europe, and likewise none attributed to those products approved in the US under 505(b)(2) of FFDCA.

   While the populations using these products remains small due to their approvals being comparatively recent, their careful evaluation pre-approval and the intense oversight subsequently makes it highly likely that any safety issues, were they to occur, will be very rapidly advertised. Prior to approval the biosimilars showed no side-effects beyond those also shown by the reference products.

   Quite irrespective of the few examples of biosimilars approved and marketed in Europe, and the 505(b)(2) biologics drugs approved in the US, the use of the same consistently and appropriately high science-based and data-driven regulatory standards for all biologics will make the risk of a safety or efficacy problem with any given product equally consistent. One must always caveat this conclusion with the necessary but unfortunate comment that it will always be the truly innovative product about which we know the least at the point of initial approval, and hence it will always be the new product that carries the greatest risk of an unforeseen adverse event. By definition we will not be able to learn from prior experience with similar products for these products. However the unmet medical needs that demand these products be made available as expeditiously as possible are a reminder that risk to patients must always be balanced by the benefits, and in this context while follow-ons will enable greater access and fulfill very important public health goals, we will always need to foster the innovation too. Both new products and follow-on biologics will be needed to maintain the on-going cycle of innovation and expanded access through competition that has created the dynamic pharmaceutical industry that has been so productive on the small molecule drug side. Now that biotechnology-based products form an increasing proportion of the pipeline of the innovator companies, and now that the patents are expiring, it is appropriate that we enable such competition on the biologics side too. If the same standards are applied to all products then they will not represent a greater risk to patients, but will enable greater access through lower prices.