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CALIFORNIA HEALTHCARE INSTITUTE

May 2, 2008

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
House Energy & Commerce Committee
316 Ford House Office Building
Washington, DC 20515

The Honorable Nathan Deal
Ranking Member
Subcommittee on Health
House Energy & Commerce Committee
316 Ford House Office Building
Washington, DC 20515

Dear Chairman Pallone and Ranking Member Deal:

The California Healthcare Institute (CHI) appreciates the opportunity to respond to the stakeholder questions regarding the creation of a pathway to allow the U.S. Food and Drug Administration (FDA) to approve follow-on biologics, or biosimilars.

CHI represents more than 250 of California's leading biotechnology, pharmaceutical, medical device and diagnostics companies, venture capital firms, research universities, and non-profit research institutions. California is the worldwide leader in biomedical R&D with over 2,700 biomedical companies and public and private research institutions advancing scientific knowledge and developing new diagnostics tools, treatments, and technologies addressing serious ailments such as cancer, diabetes, and HIV/AIDS, pain management, and cardiovascular, respiratory and infectious diseases. California's life sciences industry is an important engine of economic growth, employing more than 270,000 workers statewide, and leading the nation in terms of both venture capital investment ($3.2 billion) and National Institutes of Health (NIH) research funding ($3.16 billion).

Considering the complexity of genetically engineered product development and manufacturing, CHI believes that it is possible to develop a successful, science-based follow-on biologics approval pathway. We hope that our responses to the questions below will help achieve that goal.

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Science/Safety

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

   Immunogenicity is the capacity of a substance to stimulate an immune system response in the body. In some cases, this may be desirable -- proteins can be such strong provokers of the immune system that they are deliberately added to some vaccines (e.g., Hemophilus influenzae type b, pneumococcal conjugate) in which the objective is to provoke an immune response and the vaccine's bacterial base alone does not trigger adequate immune response.

   Nearly all biologic treatments and therapies stimulate some sort of immune response in the body, prompting the formation of antibodies. In most cases, responses are mild (e.g., tenderness or swelling at injection or infusion point, slight fatigue, passing rash). However, in some case, when clinically significant immunogenic responses do occur, the consequences can be quite serious, requiring hospitalization or even leading to death.

   Experience shows that seemingly minor changes in an established biologic's manufacturing or production processes may result in serious immunogenicity problems where none had existed before. Even the addition of preservatives and other excipients may interact with the active biologic or biologically derived component in ways that are unknown until used in large scale clinical settings (e.g., the recent heparin crisis). Immunogenicity is, therefore, particularly important in the context of manufacturing changes for biologics because minute product differences that are difficult or impossible to detect can lead to changes in immunogenicity, and such changes in immunogenicity can affect a product's safety and efficacy profile.

   Importantly, such effects cannot be predicted by chemical tests. Animal tests are also insufficient, because immune systems are unique across species, i.e., reactions to substances in humans are often quite different from reactions in other animals. Therefore, any biologic, whether an innovator therapy, or a "follow-on" or biosimilar product, must be tested in carefully designed clinical trials before being approved for marketing in order to detect immunogenicity that could be dangerous to patients.

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?**

   As noted above, immunogenicity levels can change with even seemingly trivial changes in a product's manufacturing process, leading to significant consequences. Therefore, because such clinically meaningful differences in immunogenicity cannot currently be evaluated through laboratory or non-clinical testing, immunogenicity testing, via clinical trials, is essential for all biologic products – both innovator products and follow-on biologics or biosimilars.

While the Food and Drug Administration (FDA) should have discretion to determine the *types* and *quantity* of clinical studies needed, on a case- by-case basis, it is both appropriate and important for Congress to require clinical testing for follow-ons, because such products are, by definition, not identical to the innovator, or reference, product.

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?**

   The FDA has indeed appropriately required clinical trials where innovators have made major process or manufacturing changes. However, in the case of a biosimilar manufacturer (and unlike that of an innovator who begins with a thorough and comprehensive knowledge of a process that has demonstrably produced a safe, effective, and high-quality, finished product), the entire practice is new and different – different cell lines, manufacturing facility, and manufacturing processes.

   For these reasons, the ability of an innovator to make changes to its own manufacturing process, subject to the FDA's comparability guidelines, is simply not analogous to a follow-on manufacturer proving "comparability" when entirely different processes, materials, and facilities are used.

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?**

   FOB applicants should be required to provide evidence of similarity, safety and efficacy as to each indication for which the reference product is approved. The extrapolation of safety and effectiveness data from one indication to another makes sense for generic pharmaceutical products, which share a chemically identical active ingredient, route of administration, dosage form, strength, and mechanism of action when compared to the innovator product. However, follow-on biologics are only similar to, not the same as, the reference product. Therefore, data supporting the approval of one indication for a biosimilar product should not be automatically extrapolated to support approval of other indications for that biologic.

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?**

   At a minimum, the new drug-safety related authorities established under the Food and Drug Administration Amendments Act of 2007 (FDAAA) should apply to follow-on biologics. Indeed, the likelihood that follow-on products will be approved on a more limited data set or under less

extensive pre-market testing than innovator reference products, strongly argues for increased attention to post-approval evaluation of follow-on products.

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?**

   As noted above, because follow-on products will be "similar" but not "identical" to their reference products, they may have different safety and efficacy profiles, including the immunogenicity profile. So it is important that legislation require assignment of a unique, identifiable name to any follow-on product so that it is readily distinguishable from that of the innovator's reference product.

   There are at least two important bases for this requirement in terms of patient, and public, safety.

   First, authorities must be able to distinguish among "similar" biologic medicines that are made by different manufacturers in order to quickly trace and address adverse events that may be attributable to either the innovator or follow-on product. In the case of a serious or life-threatening adverse event, public health officials must be able to attribute the adverse event to a specific product – and manufacturer – in order to determine the root cause of the safety concern and to communicate the potential risk of the product properly. Just as important, if an adverse event is associated with a specific biologic, public health authorities must be able to trace the specific product and identify the individual patients to whom that particular biologic was provided.

   Second, being able to distinguish each manufacturer's biologic product will prevent the inadvertent or inappropriate switching from one medicine to another without the prescribing physician's knowledge or consent. Again, because a follow-on product will be similar, but not identical, to its reference product, patients may react differently to a follow-on biologic than to the reference product. Switching back-and-forth among biologics poses risks, and patients should always be provided the specific biologic product prescribed by their physicians. However, in many states, pharmacy and dispensing rules do not always require a pharmacist to seek the prescriber's permission to substitute one medicine for another, or to notify the physician once substitution has occurred.

   In these circumstances, assigning a name to a follow-on product that is indistinguishable from that of the innovator product threatens confusion for physicians, pharmacists, and safety officials and poses potential danger to patients. Patient safety problems could undermine the public's overall confidence in biologics.

7. **Is it important that an innovator and an FOB have the same mechanism of action? Why or why not? If the mechanism of action of the reference product is unknown, should the FOB applicant be required to determine the mechanism of action and ensure that both products share the same one? Why or why not?**

It is essential that a follow-on product have the same mechanism of action as that of the innovator reference product. Indeed, were they to have different mechanisms of action, one would not be "highly similar" to the other and therefore could not be a "follow-on." Rather, the product should be reviewed as a new and separate product under a full biologic license application (BLA).

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?**

There is no standard "variability" in biological products. Product quality, purity, potency, and consistency are established within narrow and carefully defined specification limits fixed by the manufacturer with FDA. These specifications are measured by validated assays and controlled through in-process controls applied throughout the isolation and purification of the components and the manufacture of the product. Each batch of product must conform to these established specifications, and this must be demonstrated by reproducible results of validated analytical techniques. When a manufacturer makes changes to the process, the product must be shown to conform to these specification limits. Changes in the product or in the specifications, including product characteristics that fall outside of the established specifications, after a manufacturing change may result in FDA requiring additional analytical or clinical data to demonstrate that the resulting product will not differ in safety or efficacy from the original and, if such data are not sufficient, even requiring a new application. The manufacturer of the original product has the advantage of its intimate knowledge of the entire process. This knowledge will not be available to a follow-on product manufacturer, who will need to establish its own specifications and produce product that meets those, while still being able to demonstrate high similarity to the reference product.

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

As stated above, while the FDA should have discretion to determine the *types* and *quantity* of clinical studies needed on a case- by-case basis, it is both appropriate and important for Congress to require clinical testing for follow-on biologics, because such products are, by definition, not identical to the innovator, or reference, product. The standard for FDA approval of follow-on products, as with innovator products, should be based upon the appropriate level and type of data required to ensure the safety and efficacy of the product, not in reducing the time to market.

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?**

The very few protein products approved under section 505 based on reference to an approved product under section 505(b)(2) have generally required clinical trials to support their approval. In

general, under 505(b) an application must include (among other things) "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."

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?

This question is best answered by the manufacturer itself.

Regulatory/Administrative

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

   Although there are biologics that are regulated under the FDCA, their placement under NDA authorities was essentially ad hoc and idiosyncratic, and it does not reflect a deliberate decision on the part of the agency to subject these products to a different standard or process, particularly for follow-on approvals. Rather than perpetuating this peculiar bifurcation, Congress should consider this opportunity to consolidate all biologics in one framework. Handling all follow-on products under a single scheme would also be consistent with the approach in the European Union.

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?**

   As noted above, the FDA has indeed appropriately required clinical trials when innovators have made major process or manufacturing changes. Patient safety has, therefore, continued to be safeguarded.

3. What FDA office should review FOBs?

A follow-on product should be reviewed in the same FDA Review Division that reviewed the reference product. The scientific expertise in the original Review Division is critical to ensuring safety and efficacy of the follow-on product.

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?**

   Assessment of a follow-on biologic should require that it manifests no clinically meaningful differences, in terms of safety, purity and potency, when compared to the reference product as demonstrated through appropriate clinical trials.

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

   The FDA should be required to formulate standards for follow-on biologics through regulation or scientific guidance, providing for public comment, prior to product review and approval.

   Requiring the promulgation of regulation or scientific guidance documents would ensure that the complex scientific issues surrounding follow-on biologics are appropriately and carefully considered. Furthermore, such a requirement need not delay the consideration of follow-on biologics by the agency. The process in Europe provides an example of the value of such a model, where scientists and other experts were engaged in the development of guidelines completed in less than two years.

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?**

   While we have no specific answer to this question, we do note that industry user fees constitute a large, and growing, percentage of FDA funding. As recent reports, such as *FDA Science and Mission at Risk*, indicate, the lack of adequate *appropriated* resources has resulted in a significant erosion of the scientific foundation of the agency, threatening its ability to meet current or emerging responsibilities. Therefore, careful consideration should be given to how to best ensure adequate agency funding for the implementation of a follow-on biologics program.

Interchangeability

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

The terms interchangeability and substitutability often are used as synonyms for one another. This is misleading. We use the term "substitutability" to mean that a different product (such as a generic drug) may be substituted for the product prescribed for the patient (such as the innovator reference drug), without consultation with, or agreement by, the prescribing physician. In other words, a pharmacist may dispense the generic product automatically, substituting it for the brand product. Health plans may require dispensing of the generic or require different co-payments or reimburse differently if the branded product is dispensed instead of the generic and some State pharmacy laws may require substitution -- dispensing a generic product. Such "substitution" is considered to be safe for patients based on the fact that FDA has made a determination that the generic product is pharmaceutically equivalent to the branded product. Therapeutic equivalence is determined based on the facts that the generic product has the same active ingredient as the brand product and is shown to be bioequivalent to the brand product.

Biological products, and even complex, extremely large polysaccharides derived from biologic sources, differ significantly from small-molecule drugs in terms of the ability to assume or demonstrate "sameness" of the active ingredient. Because these products derive from biological systems, they are inherently "different," as all biological systems are different. Therefore, unlike generic drugs, follow-on biologic products will not and cannot be assumed to have the same active ingredient. Therefore, the demonstration of the clinical effects of these products will be essential and will need to include many more data and significantly different studies than simply demonstrating bioequivalence.

It is crucially important for patient safety (both in terms of potential adverse events and in terms of product effectiveness) that physicians clearly understand differences among products they prescribe and that dispensers not change the physician's decision by automatically dispensing ("substituting") another product, unless it is clear that the two will have the same effect and the patient will not suffer from the product switch (presumed to be the case if, and only if, FDA has made a determination of therapeutic equivalence).

At the current state of scientific knowledge, with inherent differences among biologic products, it is not possible that "interchangeability," which may trigger "substitution," can be ascertained. As Health and Human Services Secretary Michael Leavitt noted in a letter to Senator Kennedy: "in light of current scientific limitations on the ability to make determinations of interchangeability ... patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician ...."[1] It is also important to note that "switching" two innovator products may also not be safe for patients, and also requires -- as is current medical practice -- an affirmative decision by the physician to prescribe one or another product, and no ability for dispensers to make a different choice without consulting with the physician.

Some might argue that without interchangeability, follow-on biologics will be ineffective in improving patient access through increasing choice and potentially reducing cost. This has not been the case with biosimilars already approved in Europe, and will not be the case in the US. As with competing products in the market today, including multiple versions of innovator biological products

[1] June 26, 2007 letter from Michael O. Leavitt, Secretary of Health and Human Services, to Senator Edward M. Kennedy. p. 5.

such as insulin, human growth hormone, and the interferons, physicians choose what is best for their patients and health plans decide how to cover the costs of products, based on a variety of medical and economic factors, and the market is shared. Because follow-on biologics presumptively will not need as large or complex a data package as was required for the innovator product and because follow-on biologics manufacturers will not have to commit as significant an amount of resources to research and development of the product (since their FDA approval will "ride," to some extent, on data already provided by the innovator), their costs can be expected to be lower than those of the reference innovator. (However, because substantial data will be needed, including clinical data, and manufacturing costs will be high, cost decreases on the order of generic drugs are unlikely). This cost differential, the quality and robustness of the data, and the decision of the regulatory agency all will be factors than can help companies garner market share.

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

   As noted above, given the complexity of biologic products and the possibility that there could be clinically significant differences between a follow-on product and its reference product, determinations of "interchangeability" for biologics would be extremely problematic if not impossible at this time.

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.**

   As stated above, and as noted by the FDA itself, determinations of interchangeability between biologics would be extremely difficult, if not impossible.[2] However, if such determinations are permitted, it is important that legislation require the FDA to formulate scientific standards through a clear, public product-specific guidance process.

   Regardless, and consistent with the policies of the EMEA and every European country that has addressed this issue, Congress should prohibit follow-on products from being given to any patient unless expressly prescribed by a physician, in order to avoid inadvertent or unknowing substitution.

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?**

   Yes, if determinations of interchangeability are permitted, it is important that legislation require the FDA to formulate scientific standards through a clear, public product-specific guidance process in

[2] "With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins." http://www.fda.gov/cder/news/biosimilars.htm, Possible International Non-proprietary Name (INN) Policies for Biosimilars, September 1 2006.

order to ensure full and careful consideration of the views and expertise of industry, scientists, physicians, patient groups and others.

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?**

   Please see the above response to question #1 in this section.

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

   Theoretically, in any field as the number of companies producing an "interchangeable" product increases, the price would generally decrease. However, given the complexities and high costs involved in the manufacturing of biologics, it is questionable how significant the impact would be in this instance.

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?**

   While numbers vary, at least three studies provide insight into the question.

   A 1998 Congressional Budget Office report found that the average period of time for marketing of a drug product with patent protection is 11½ years.[3] A 2003 study by economist Henry Grabowski investigated new chemical entities (NCEs) put on the market between 1991 and 1995 and found that those products had an average effective patent life of 11.7 years, which included, on average, a Hatch-Waxman patent term extension of 2.3 years.[4] A more recent Grabowski study found that new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.[5]

[3] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

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

[5] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics Volume: 28. Issue: 4-5. Pages: 491-502. 2007.

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?**

   The Hatch/Waxman Act provided for a mechanism balanced between incentives for innovation and entry of generic pharmaceutical products to the marketplace. However, because of the fundamental differences between small molecule products covered by Hatch/Waxman (generic drug generally identical to the reference product and likely to fall under the reference product's patents) and biologics covered by any follow-on pathway (product similar, not identical, to the reference product and less likely to be fully covered by reference product patents) the mix of policy tools for a biosimilars approval mechanism will, likewise, be fundamentally different.

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?**

   While patent protections are fundamental to biotechnology investment, development and innovation, in the context of a biosimilars framework, they are not adequate alone. In particular, because a follow-on product will be similar but not identical to its reference product, any patents that cover the reference product may not cover the follow-on product. The risk that a follow-on manufacturer can claim its product is similar enough to rely upon the innovator's data in seeking approval, but different enough to avoid patent infringement will result in an increased level of uncertainty that will undermine private investment in biotechnology. Therefore, with the establishment of a biosimilars pathway, while patent protections will remain fundamental to biotechnology investment and innovation, data exclusivity protections will be even more important. Specifically, a longer period of data exclusivity is necessary for biologics than that offered for pharmaceuticals under Hatch/Waxman.

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?**

   It is critical that any biosimilars legislation provide for a mechanism facilitating resolution of patent disputes between follow-on applicants, innovators, and any third-party patent holders before a follow-on product comes to market.

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?**

   Both the third-party patent holder and the reference product sponsor require sufficient notice of applications for follow-on products that might implicate their patents. As the history of

biotechnology has shown, many scientific breakthroughs have been licensed to the private sector for commercial development by California's world-class universities and private research institutes. Protecting the patent rights of third-party patent holders, such as these, is a significant priority.

6. **Should an FOB statute require FDA to administer patent listing and notification provisions as Hatch-Waxman does? Has this process been an appropriate and efficient use of FDA's resources and expertise? Why or why not? Can appropriate notification be accomplished through an alternative process that does not enlist FDA resources**?

   No, any follow-on biologics statute should not require FDA to administer patent listing and notification provisions as is done under the current Hatch-Waxman Act. There is no technical need for FDA to be involved in a patent identification process, so therefore, it would be more viable and efficient for the legislation to provide for a direct exchange of patent information between patent owners (innovator company and any third party holders) and biosimilar applicants.

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?**

   As mentioned above, with the establishment of a biosimilars pathway, while patent protections will remain fundamental to biotechnology investment and innovation, data exclusivity protections will be even more important. Specifically, 14 years of data exclusivity (not an "exclusive marketing" period) protections are necessary to provide sufficient incentives for continued innovation.

   It is important to distinguish "data exclusivity" from "market exclusivity." Data exclusivity refers to the period of the time during which innovator companies have exclusive use to their proprietary data, generated to support a finding of safety and efficacy of a product by the FDA. Market exclusivity provides a product exclusive access to a market and currently exists only within the context of the Orphan Drug Act. Under current law, multiple biologic products can in fact compete in the same market space, provided each submits a complete BLA to the FDA with all necessary data, and assuming the FDA finds each product to be safe and effective.

2. **What types of assessments have been conducted to determine the minimum term of exclusivity that will enable a robust industry for discovery and development of biologics?**

   To ensure continued biotechnology innovation, companies, venture capitalists, and others must be certain that they will have adequate time and opportunity to recoup their substantial investments. It can cost over $1 billion and take 10 to 15 years before a new product can progress from the lab, through the arduous FDA approval process, to patients in need. According to economist Henry Grabowski, the breakeven point for a biologic occurs after it has been on the market between 12.9

and 16.2 years.[6] If a company does not have adequate time to recoup its investment, it will not engage in the research and development of future products.

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

In addition to the significant investments made by companies in initially developing a biologic product, companies often incur significant additional expenses in order to modify and improve an approved product. An example is in the area of oncology, where the initial product marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies typically follow. In order for promote and protect these advances, robust data exclusivity must be provided.

Therefore, if an approved product is subsequently approved for a medically significant new indication during its original period of data exclusivity, the innovator should be granted a limited additional period of data exclusivity as an incentive to conduct additional research on existing molecules. Similarly, approval of a pediatric indication should also result in the granting of a limited period of additional exclusivity.

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

Patents protect the initial discovery – the molecule, or process for making a product -- and typically are issued very early in the research and development process. In fact, a patent application may be filed before it is even known whether the discovery has commercial potential. Data exclusivity, however, serves to encourage companies to undertake lengthy, costly, and risky product development efforts needed to receive FDA approval.

As discussed above, given the differences between biologics and traditional small molecule pharmaceuticals, particularly with respect to the scope of patent protection, a follow-on product sponsor may be able to obtain FDA approval in reliance on the clinical safety and efficacy of the reference product, yet avoid infringing the innovator's patents. Given that uncertainty, therefore, only data exclusivity can adequately protect an innovator from imminent follow-on competition.

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

Yes. As addressed above, unlike traditional drugs a follow-on product will only be similar, not identical, to its reference product. Therefore patent protections alone will not suffice and the period of data exclusivity for biologics should be different (i.e., longer) than that of small molecule pharmaceuticals as provided under Hatch/Waxman.

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

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

   As noted above, while patent protections are fundamental to biologics and drug investment, development and innovation, in the context of a biosimilars framework, they are not adequate alone. For biologics, data exclusivity protections will be more important.

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?**

   If a follow-on pathway were created based on patent protections alone, without any data protection for innovator products, innovation would suffer. In particular, the thousands of small firms making up the majority of the biotechnology industry would see venture capital funding shrivel as VC firms turn to other less risky investments. Universities and private research institutes would suffer from less favorable terms in licensing promising technologies, since companies would not be able to recoup the costs necessary to further develop and market a product. And research and development decisions by larger, more established and self-funding biotech companies would likewise be affected. In total, without adequate intellectual property and data exclusivity protections, biomedical research and development will suffer.

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**.

   A number of studies exist which purport to establish the savings that would accrue from the establishment of a biosimilars, not a "generic biologics," pathway. One, by Express Scripts, projects $71 billion in savings over a 10-year time period. Another, by Avalere Health, suggests a more conservative level of $3.6 billion in savings over 10 years.[7] These wildly different estimates suggest that the Congressional Budget Office (CBO) should be asked to study the question and score the bills introduced on the subject.

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**

[7] The Express Scripts study is available at http://www.express-scripts.com/industryresearch/outcomes/onlinepublications/study/potentialSavingsBiogenericsUS.pdf. The Avalere Health study is available at: http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf

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?

N/A

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

   The United States, and California in particular, leads the world in biotechnology research, development, and innovation, developing the next generation of treatments, therapies, and technologies in areas including cancer, diabetes, Alzheimer's, HIV/AIDS, and many others. The industry is also an important engine of economic competitiveness and growth, with 2,700 companies employing 270,000 people in California alone. The enactment of a follow-on biologics pathway that properly recognizes the importance of patent and data exclusivity protections to promoting continued research and investment in this exciting, but still young and fragile industry, promises to maintain and strengthen U.S. leadership in this important field.

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?**

   Patent protections, and in particular a robust mechanism for facilitating timely resolution of patent disputes among innovators, biosimilar applicants and third-party patent owners prior to approval of a follow-on product, are a very important element of a successful follow-on biologics pathway and continued biotechnology innovation.

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

   The importance of robust and vibrant university research to the biotechnology industry can been seen in a number of ways. It is by no accident that, in California for example, biotechnology clusters have developed around research university and institute-rich areas such as the San Francisco Bay (e.g., Stanford and the University of California at San Francisco.) and San Diego (e.g., UC San Diego, The Salk Institute for Biological Studies, The Scripps Research Institute, e.g.). In fact, one in four public biotechnology companies are within 35 miles of a University of California campus and fully one-third of California biotechnology companies were founded by University of California scientists.

   Research flows from universities to the private sector through technology transfer and licensing agreements. The private sector, as addressed above, then incurs the significant risks and costs in terms of time and capital to further develop the technology into an approved and marketable product.

Upon success, universities and private research institutes receive royalties that, by law (Bayh-Dole), are reinvested into additional research and education activities.

Failure to include ample incentives in a follow-on biologics pathway, in terms of patent and data exclusivity protections, would undermine this successful partnership and stifle the transfer of promising university-discovered technologies to the private sector.

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.?**

   Given the successful implementation of a transparent, public process for the development of biosimilar guidelines in Europe, industry, healthcare providers and patients here in the United States would most certainly benefit from a similarly required framework in U.S. law.

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?**

   While this framework of exclusivity in the European system may be appropriate there, given the role of the U.S. biotechnology industry as the global leader, and the importance of maintaining and strengthening that position, data exclusivity protections should be longer in the United States than in Europe.

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

   The likely effect would be that the United States' position as the global leader in biotechnology research and innovation would be substantially weakened. This would hold particularly negative consequences in terms of economic growth and job creation in a biotechnology-rich state like California.

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

The European experience shows that a science-based pathway for the review of follow-on products is possible, and necessary for patient safety. It is generally a good model for a biosimilars pathway here in the United States. In terms of patient safety considerations (including interchangeability) specifically, the European Medicines Agency (EMEA) recently issued a statement that "[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."[8] Furthermore, with respect to the requirement for clinical trials, EMEA's product-specific guidelines to date make it clear that the agency will require clinical data, for example with respect to immunogenicity, in every case.

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?**

   We are aware that at least one product (ALPHEON, a follow-on interferon alpha-2a for Hepatitis C) was rejected in Europe after required clinical studies showed that it was not as pure as the reference product and had more side-effects.

   In 2006, a generic calcitonin (rDNA), manufactured via a recombinant process, was rejected for approval in the U.S. because of agency concerns over possible immunogenicity due to the addition of a preservative in the formulation. To date, this product is still not approved and its status is unclear.

Thank you again for the opportunity to respond to these important questions surrounding the creation of a pathway to allow the U.S. Food and Drug Administration (FDA) to approve follow-on biologics, or biosimilars. Please do not hesitate to contact me, or Todd Gillenwater, CHI Vice President for Public Policy, if we may be of any further assistance.

Sincerely,

David Gollaher

David L. Gollaher, Ph.D.
President & CEO

[8] EMEA document available at: http://www.emea.europa.eu/pdfs/human/pcwp/7456206en.pdf