

**Statement of the
California Healthcare Institute (CHI)**

**Submitted to the
U.S. House of Representatives
Subcommittee on the Courts and Competition Policy**

**Hearing on:
Biologics and Biosimilars: Balancing Incentives for Innovation**

Tuesday, July 14, 2009

The California Healthcare Institute (CHI) appreciates the opportunity to present our views on the issue of biologics and biosimilars for this important hearing.

CHI represents more than 250 of the state's leading biotechnology, pharmaceutical, and medical technology companies, venture capital firms, and premier academic research institutes and universities. CHI's mission is to identify and advocate for policies to promote biomedical research, development and innovation in California. The California life sciences industry, employing over 270,000 workers, is responsible for medical breakthroughs that are improving and extending the lives of millions in the United States and around the world.

While focused on the development of the next generation of innovative medicines, we understand that the increasing cost of health care is a growing burden for private-sector and government budgets. In the long term, competition among biosimilar products is likely to yield savings within the U.S. healthcare system. Considering the complexity of large molecule product development and manufacturing, CHI believes that it is possible to develop a successful, science-based FOBs approval pathway. This pathway must employ the best science to make sure that products are safe for patients, encourage price competition among manufacturers, and provide ample incentives and intellectual property protections to encourage continued private-sector investment in the next generation of breakthroughs.

CHI has endorsed H.R. 1548, the Pathway for Biosimilars Act, introduced by Representatives Anna Eshoo (D-CA), Jay Inslee (D-WA), and Joe Barton (R-TX) as best reflecting these important principles.

Follow-On Biologics: Enhancing Development of New Biologics Introduction

The term “biologics” refers to a broad range of therapeutic biological products, typically large, complicated molecules produced by biological processes.¹ The introduction of biologics has greatly affected the treatment of a wide array of diseases, including cancer, arthritis and autoimmune diseases and holds great promise for future therapeutics. However, these therapeutic agents can be very expensive. To address the expense of biologics and provide access to consumers, Congress is considering legislation that would create an approval pathway for biosimilars, or Follow-On Biologics (“FOB”) – products that are claimed to have similar properties to existing biologics. FOBs are thus analogous to the generic version of a traditional chemical pharmaceutical. However, biologics are produced by culturing living cells as compared to traditional “small molecule” pharmaceuticals that are synthesized chemically. As such, an FOB could never be identical to the existing biologic it attempts to copy.

The development of biologics requires input of large amounts of time and money for the initial development and the lengthy clinical trials required to bring the product to market. Without a system to protect the investments necessary to develop biologics, companies and universities may be averse to inventing and commercializing new biologics. A traditional mechanism for protection of intellectual property (IP) has been the patent system. However, patents covering biologics are typically more limited in scope than those granted for traditional pharmaceuticals and seem insufficient to protect the full scope of investment by biologics innovators. To foster development of emerging biologics, an FOB regulatory approval system put in place by Congress should provide sufficient protection to provide strong incentives for biologics innovators to invest time and money into developing biologics. It is this regulatory system that will provide for the avenue for continued innovation in critical future therapies while also providing for increased price competition.

Approval of Generic Drugs

The Hatch-Waxman Act provides for a regulatory approval scheme for generic versions of innovators’ pharmaceuticals, which are typically small molecules, produced chemically to be exact copies of the approved drug.² When filing an Abbreviated New Drug Application (ANDA), the applicant must show that the generic version of a pharmaceutical has both pharmaceutical equivalence – same active ingredients, strength, and dosage form – as well as bio-equivalence to the innovator pharmaceutical.³ Upon such showings, the ANDA applicant is permitted to rely upon the safety and efficacy testing performed by the innovator producer. The Hatch-Waxman Act provides for five

¹ Section 351(i) of the Public Health Service Act (PHS Act) defines a biological product as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound.”

² 21 U.S.C. 505(j)

³ 21 C.F.R. §314.92

years of data exclusivity⁴ following approval of an innovator's drug,⁵ during which time the Food and Drug Administration (FDA) will not allow an ANDA applicant to rely on an innovator's clinical efficacy and safety data. This regulatory scheme was designed for small molecules, as is clear from the requirement that a generic product must have the same active ingredient as the innovator's product – something that is not possible with biologics.

Currently, most biologics are regulated through the Public Health Service Act, which does not provide for an abbreviated application process such as that for small molecules under the Hatch-Waxman Act. Thus, there is no equivalent for the approval of an FOB as a "generic" version of a biologic. Multiple bills have been introduced in Congress to provide such a regulatory approval process.⁶ While each bill differs in the particulars, most bills recognize the need for different treatment of biologics from the Hatch-Waxman scheme.

As a consequence of the differences between small molecule drugs and biologics, two key issues have surfaced for any follow-on biologics legislation: 1) what showings are necessary to establish similarity to the biologic to permit use of the FOB instead of the approved biologic (interchangeability and/or biosimilarity), and 2) for what period of time is the FOB not permitted to use the data that was generated by the innovator to gain FDA approval of the biologic (period of data exclusivity).

Biosimilarity

Generics of small molecule drugs are exact chemical duplicates of the approved innovative pharmaceutical. However, it is unlikely that a manufacturer of an FOB will be able to produce an identical active ingredient to an approved biologic due to the complexity of biologics and the resulting changes in the biologics stemming from innate differences between the cells and growth conditions utilized to produce biologics. Indeed, biologics such as proteins are variable and complex and are difficult to consistently manufacture. Because of these difficulties, an FOB manufacturer attempting to produce an FOB identical to an approved biologic would be unable to do so.⁷ Thus, a major difference between the proposed legislation and the Hatch-Waxman Act is that FOBs, unlike generic small molecule drugs, need only show "biosimilarity," not complete identity with the innovator's biologic. For a biosimilar, small differences are likely to exist in properties such as pharmacokinetics, pharmacodynamics, and immunogenicity profile. Exactly what showings will be required – how similar the FOB must be to the approved biologic, and whether or what clinical trials will be necessary to

⁴ The period of time during which a generic / FOB manufacturer may not refer to the pre-clinical and clinical trial data of the originator, usually beginning after approval of the innovator's product. Under Article 39.3 of the TRIPs Agreement, data exclusivity is considered an intellectual property right

⁵ This period may be shortened to four years if a Paragraph IV certification is filed.

⁶ These bills include: 1) the "Access to Life Saving Medicine Act" (S. 726 and H.R. 1427); 2) "The Pathway for Biosimilars Act" (H.R. 1548).

⁷ Woodcock, "Follow-On Protein Products," 2007 (statement before the Committee on Oversight and Government Reform, U.S. House of Representatives) available at <http://www.fda.gov/ola/2007/protein32607.html>.

establish biosimilarity, safety and approval of interchangeability – is an issue to be resolved. Because the FOB and innovator’s product will not be identical, they will not be “interchangeable” or will not be substitutable one for the other without the approval of a physician, at least initially.

The difference between “biosimilarity” in the proposed FOBs approval legislation and chemical identity under the Hatch-Waxman regulatory scheme, affects the ability of innovators to fully protect investments using the patent system. Because an FOB would not be identical to the approved biologic and need only show biosimilarity, an FOB would have significant latitude for slight molecular changes that would retain “biosimilarity” but fall outside the scope of the patents covering the approved biologic. The more dissimilar the FOB is to the innovator’s biologic, the less likely that patent infringement could be proven. The large size of biologics increases the likelihood that an FOB will contain a difference that would preclude a finding of infringement. For example, if an innovator’s patent claims cover a protein with a particular amino acid sequence, numerous changes could be made to that sequence while retaining biological equivalence or biosimilarity, but could avoid infringement of the innovator’s patent.⁸

Patent Protection for Biologics

As with many areas of innovation, patent protection for biologics is important for fostering investments in the research and development of potentially life-saving biopharmaceuticals. However, a number of factors diminish the ability of patents to provide a level of coverage adequate to ensure continued investment in and development of the critically important biological pharmaceuticals. One factor is that the patent protection currently being afforded to biologics has become limited in scope and challenging to obtain. Additionally, the length of enforceability after lengthy prosecution before the United States Patent and Trademark Office (USPTO) and FDA approval can significantly reduce the time for recouping development costs. Another factor is that the patent enforcement provisions of the Waxman biosimilars legislation bill would undermine the value of biologics patents that are obtained.

Limited Patent Scope

Although biologics can potentially be protected by a multitude of patents covering products, methods of making the biologics, and methods of using the biologics, claims to the precise biologics have become increasingly narrower. Patent claims to small molecules frequently can cover a particular molecule and a large genus encompassing that molecule, thus providing protection for the drug and numerous variants. Such broad genus claims typically are not available for biopharmaceuticals, and an innovator may

⁸ The Doctrine of Equivalents, which allows for a finding of infringement where an accused product does not literally infringe the claims, but comprises only minor deviations has been strongly curtailed by the Supreme Court and the Court of Appeals for the Federal Circuit. *See, e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722 (2002) (holding that narrowing a claim for reasons related to patentability causes the patentee to lose equivalents to the limitation narrowed, except those unforeseen at the time of the amendment).

need multiple patents to cover a fraction of the scope available for small molecules. In a typical prosecution at the USPTO, a broad genus claim to a biologic will be narrowed to a more limited genus or species by restriction and/or rejection as being too broad and failing to provide an adequate disclosure to support the claims to the broad genus. In order to obtain some protection for the biologic, applicants will often accept quite narrow claims and then refile continuations or divisionals to prosecute broader claims or claims drawn to another aspect of the invention. The amendment to narrow the claims may surrender the broader concepts and reduce or eliminate the ability of patentee to later assert during litigation that a biosimilar or close equivalent infringes the claims.

These differences in scope of protection between small molecules and biologics result from the application of the patent laws as interpreted by the courts and the examination practices in the USPTO, including restriction or limitation of the claims to a single claimed invention. In many cases, a biotechnology invention includes a protein, the DNA encoding the protein, the cloned protein and a monoclonal antibody which binds to the protein. However, through restriction of claims, the USPTO usually permits the coverage of only one of these facets of the innovation per patent, thus resulting in multiple patents if the innovator wishes to cover each facet. Additionally, unlike small molecules, typically the innovator is not able to claim a genus consisting of a large number of molecules within any of these groups. This result arises from court interpretations of the law concerning written description⁹ and enablement,¹⁰ and the amount of disclosure necessary to support the claims. While these rejections are being applied by the examiners in the USPTO more frequently in all technologies, they are applied routinely and stringently in biotechnology.

One reason for this may be that biologics are often claimed in terms of function, while small molecules are claimed as a structure. For example, a claim might be directed to an isolated DNA that encodes a polypeptide with at least 85% amino acid identity to sequence X, wherein the polypeptide has activity Y. Such a claim will be rejected by the USPTO as lacking adequate written description of the genus unless there is significant disclosure concerning a structure-function relationship between the necessary structure of the variations of sequence X which still retain the function or activity Y. Thus, without sometimes extensive additional experimentation and examples of specific changes that may be made to the amino acid sequence or detailed explanations of the structures necessary for the functions and those areas of the sequence which may be changed, the applicant will be limited to a narrow scope of disclosed sequences. In contrast, a small molecule is frequently claimed as a genus chemical formula with numerous variations of substituents on the core chemical structure with the USPTO raising written description or enablement concerns much less often. Thus, patent claims

⁹ To satisfy the written description requirement of 35 U.S.C. §112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention at the time of filing the patent application.

¹⁰ 35 U.S.C. § 112, first paragraph requires that a patent application describe the invention in such terms that one skilled in the art can make and use the claimed invention, thereby insuring that the invention is communicated to the public in a meaningful way.

for biologics with limited scope provide limited protection for innovators and may allow opportunities for avoiding infringement.

Length of Enforceability

Several factors play a role in diminishing the period of patent enforceability for biotech patents. These factors include: (1) evolutionary development of biologics and the 20-year patent term, (2) significant prosecution time for patent allowance, and (3) FDA approval time. In biotechnology, it is common for the original innovations to occur in academia and subsequent developments to occur with a company licensing the patent(s) obtained by the university. For example, the original patent may disclose a protein or biomarker associated with a disease, the DNA encoding the protein, and cloning of the protein. The company licensing the foundation patents or another larger company may then develop advances on the original innovation, such as specific antibodies to the protein for therapy of the disease. During this period of development, the 20-year patent term is running from the original patent filing. For subsequent evolution and development of treatment of other indications or improvements, a new patent term may exist.

It often takes a considerable amount of time to prosecute an application to allowance, sometimes requiring a number of continuation applications to reach agreement with the examiner as to allowable subject matter. As noted above, the application of the enablement and written description rejections against the claims necessitates extensive arguments and often evidentiary showings to establish patentability. This takes considerable amounts of time, all while the clock is ticking on the patent term.

Also, for both biologics and small molecules, significant time is required for all of the analyses and clinical trials required for FDA approval. While it is possible to recover up to 5 years of patent term for these regulatory delays, there may not be an adequate period to recoup the costs of the research and development of the biologic. The cost of performing the research and development necessary to produce a biopharmaceutical is very high. One analysis has estimated that the total out of pocket expenses for preclinical and clinical trial periods for a new biological entity range from \$1.24 to \$1.33 billion.¹¹ Additionally, the period from initial discovery of a biological disease target through discovery and testing of a biologic to approval by the FDA can take decades. One well-described instance of this lengthy period involves the biopharmaceutical Avastin®. From the initial discovery of Avastin's® target (vascular endothelial growth factor) to the approval of Avastin® by the FDA, fifteen years elapsed.¹² As a consequence even with the patent term extension provision of up to five years, patents may be inadequate to provide the necessary period of exclusivity needed to incentivize investment in this area.

¹¹ Capitalized costs adjusted for inflation over time. DiMasi and Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Econs.*, 28: 469-479 (2007).

¹² Flanagan, "Avastatin's Progression" *Bio Century*, 14(11): A1-A5 (2006).

Patent Enforcement

Currently, there are legislative proposals for developing an FOB regulatory scheme, including proposals by Representatives Waxman and Eshoo. These bills differ in some particulars, including several aspects that may affect patent value. One such aspect is the time period during which the FDA could accept abbreviated applications – under the Waxman bill an application could be filed at any time, whereas under the Eshoo bill, an application could be filed only after four years have passed since the innovator product was approved. Another aspect is the length of time for data exclusivity – the Waxman bill provides a period of 3 or 5 years and the Eshoo bill provides for 12 years. Other aspects include provisions for multiple indications – the Waxman bill would allow use of the FOB for all indications even if the FOB applicant sought approval for one indication, whereas the Eshoo bill would require approval for all indications – and would require product nomenclature. While each of these differences affect the potential value of patents held or licensed by the innovator, the differences in the patent enforcement provisions of the two bills would result in drastically different effects on such value.

The Waxman bill's patent enforcement provisions are skewed in favor of the FOB applicant and would allow an FOB applicant, or prospective applicant, to request patent information from the innovator as to all patents owned or licensed which the innovator "believes in good faith relate to the reference product." Any patent erroneously not listed in response is thereafter unenforceable against anyone, even if the patent is held by a third party – in effect, the patent loses all value. Unfortunately, the Waxman bill does not define what the term "relate to" means. Furthermore, under the Waxman bill, the FOB applicant would determine, based on the listing by the innovator, which and how many of the patents would be litigated. Thus, under the bill's provisions, the FOB applicant could challenge a listed patent for any reason, even if that patent would not actually block the FOB. The Waxman bill also allows an FOB applicant to serially respond to the innovator, potentially resulting in multiple patent suits. Timing of litigation (i.e., pre-launch litigation) and venue would also be entirely under the control of the FOB applicant. Such a system, far from streamlining and simplifying the litigation process, would allow for excessive gamesmanship on the part of an FOB applicant. Additionally, potential abuse of the Waxman enforcement procedures could create serious problems for third-party patent holders – such as universities and small biotech companies – who could lose all rights in their patents and, thus, lose an important research revenue stream.

In contrast, the Eshoo bill provides that those patents held or licensed by the innovator which would be available for a declaratory judgment action would be limited to those identified by the innovator or third-party patent owner as covering the FOB. A determination of which patents "cover" an FOB would be determined by the innovator or the third-party after analysis of the abbreviated application, information about the product and its method of manufacture. All such information would be treated as confidential and the analysis would be provided to the FOB applicant. The innovator and/or third-party would have 60 days to file suit. If no suit is filed, then the applicant could file a declaratory judgment action, if there are three years or less remaining in the approved

product's exclusivity period. In short, the Eshoo bill more strongly recognizes the importance of maintaining patent rights.

Encouraging investment in innovators

In order to foster investments in the discovery and development of new biologics, biotechnology companies must have some certainty that innovative biologics they produce will yield a return on initial investments, including costs and some profit. Currently, most U.S. biotechnology companies are small start-up companies that do not have a product on the market and thus have little or no revenue stream. In a recent survey of small biotech firms conducted by the Biotechnology Industry Organization, 65% of the companies had fewer than fifty employees and 40% had revenues less than \$150,000.¹³ For many such companies, their intellectual property – in the form of patents or data exclusivity – is the only asset of real value. Such companies rely heavily on venture capital investments to produce the innovative biopharmaceuticals that are the cutting edge of medical treatment. Often eventually acquired by a larger company, these small companies have become the source of the important biologic pharmaceuticals and innovation.

To provide incentives for companies and their venture capital financiers to engage in such high-risk new biologic development, it is necessary for there to be some certainty of return on investments. In other words, a biosimilars regulatory scheme needs to supply some certainty regarding the protection provided by the innovator's patents and, potentially, further safeguards. Without sufficient patent protection and reasonable patent enforcement for innovators, FOB producers will be able to establish biosimilarity, rely on the innovator's data for FDA approval, and avoid infringing the innovator's patents. Such results would lead to fewer investments in new biologics because of the lengthy time that it takes to get a biologic approved after the initial discovery is made and the staggering costs of developing biologics.¹⁴

Conclusion

The cost of cutting-edge biopharmaceuticals can be prohibitive for some patients. To address this concern, Congress is considering developing a regulatory scheme to allow for the approval of "generic" biopharmaceuticals, more accurately known as biosimilars or follow-on biologics. While the need exists to lower patient costs and provide more people with access to biopharmaceuticals, it is also important to protect the investments of time and money by innovators so that new biologics, and new uses for existing biologics, continue to be discovered and developed. The patent system may not provide sufficient protection to these innovators because of limitations on scope and

¹³ Available at http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

¹⁴ Expenditures in excess of one billion dollars on average must be made for new biologic development, despite the fact that biologics have a lower probability of success in Phase III trials, higher discovery and pre-clinical expenditures, and longer clinical development times than traditional small molecule pharmaceuticals. Grabowski, "Data Exclusivity for New Biological Entities," June 2007; available at <http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf>.

length of patent coverage for biologics. Furthermore, the ability of an FOB to gain FDA approval if it is only “biosimilar” further compounds the likelihood that an innovator’s patents will not adequately protect its investments. Additionally, one of the legislative proposals for a regulatory scheme for follow-on biologics would provide the opportunity for litigation gamesmanship and undermine future investments and likelihood that an innovator will invest time and money into developing new biologics. Without adequate protection of investment through patents and/or data exclusivity, which CHI believes is best provided through H.R. 1548, fewer new biologics will be developed, effectively cutting off access to such innovations for all persons, undermining the initial concern of Congress in developing an FOB regulatory scheme.