

Biosimilar Legislation and its Impact on IP Protection

Tracy Huang, Zheng Liu, Elizabeth Howard, and Deborah Fishman¹



About Authors: Tracy Huang is currently a Licensing Associate at Yale University's Office of Cooperative Research, and was previously with the Massachusetts Institute of Technology's Technology Licensing Office. Tracy also has IP strategic business experience through her tenure at Global Prior Art, Inc. in Boston, MA. Tracy holds her bachelor's degree from MIT, where she also conducted research at the Whitehead Institute, and was an intern at both Biogen Idec and Massachusetts General Hospital. Tracy also holds a M.S. from Yale University.

Zheng (Jen) Liu, a managing associate in the Silicon Valley office, is a member of the Intellectual Property Group. Ms. Liu's practice focuses on intellectual property litigation, intellectual property counseling and technology transaction across a broad range of industries, including biotechnology, pharmaceutical, medical devices, diagnostics, computer networking and telecommunications.

Elizabeth Howard, an intellectual property partner in the Silicon Valley office, is co-chair of the Orrick life sciences practice. She focuses her practice on patent infringement litigation, with an emphasis on the life sciences. Her

Introduction

Biological products ("biologics") include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.¹ Biologics are generally much larger and more complex than the more

practice also includes trade secrets disputes and handling anti-counterfeiting matters in the pharmaceutical industry. In addition to litigating in numerous federal district courts and California state courts, Dr. Howard has appeared before the U.S. Patent and Trademark Office in interference proceedings, and arbitrated before the International Chamber of Commerce. She is listed in *PLC Which Lawyer?* - life sciences: intellectual property. The following are some of her more notable engagements.

Deborah Fishman, a partner in Orrick's Silicon Valley office, is a member of the Intellectual Property Group. She specializes in technology litigation with an emphasis on patent litigation practice. Deborah's experience also includes antitrust, trade secrets and general commercial litigation. Deborah has successfully represented Fortune 500 companies in their business-critical patent litigation and has litigated five US\$1 billion+ cases through trial. She has handled biotechnology and pharmaceutical patent litigation and has provided strategic litigation counseling and analysis for biotechnology and IT clients. Deborah also has represented clients before the U.S. International Trade Commission (ITC) in Section 337 proceedings.

conventional small molecule drugs, and, because they are the product of a biological system, far more challenging to manufacture. For example, even slight differences in manufacturing processes can alter the glycosylation of a protein and/or protein folding – leading to profound effects on the activity of the protein. As a result, this class of drugs requires significantly longer lead times on aver-

age for research and development than small molecule drugs, and the manufacturing processes are significantly more exacting and expensive. Investment in biologics thus carries tremendous risk. For these reasons, any regulatory scheme that streamlines the approval process for generic biologics (also called “follow-on biologics” or “biosimilars”)² must also provide for a sufficient period of exclusivity for companies who develop the biologics drugs from the beginning (also called “reference biologics companies”) to recoup their investment – else innovation in this area will be unacceptably chilled. Further, as set forth below, the ideal biosimilar regulatory scheme should include not only a sufficient period of exclusivity for the innovator, but also provisions that adequately address intellectual property issues such as data exclusivity and confidentiality – both of which are put at risk if unaddressed. While several legislative schemes have been proposed to address biosimilar legislation, none address these key issues. If these issues are not resolved by Congress, they must instead be resolved by the courts – a result that will necessarily lead to uncertainty for years to come as the various issues wind their way through the appellate process.

Background

Healthcare reform is currently an issue of primary concern in the U.S., and an important issue in this debate is the need to identify more effective drugs, while still containing costs. Central to the idea of cost containment is a regulatory approval process for generic versions of brand name drugs to help achieve the proper balance between keeping costs down while still encouraging and rewarding innovation. Currently, the Hatch-Waxman Act³ provides an abbreviated regulatory pathway for generic small molecule drugs – thus, for small molecules, that balance has been struck. However, there is no formal regulatory pathway for biosimilars; several proposed schemes for addressing the regulation of biosimilars are presently under consideration. In this article, we focus on the details of those proposals and identify some areas of deficiencies still needing attention before any such proposal is finally adopted. In particular, we will explain the significance of the unaddressed intellectual property issues and how they may affect intellectual property protection for the industry.

Biologic Innovation Requires Huge Investments Into High Risk Undertakings

Today, the U.S. spends more than \$60 billion annually on biologics. While biologics only account for 10-15% of the total drug market—the rest being small molecules

drugs made through chemical synthesis—they are the fastest growing segment. However, they are also the segment that presents the highest risk to investors. Biologics are generally much more complex than small molecule drugs, as they are much larger; they are by definition related to a biological process (or even, as in the case of for example a cell, a biological system itself), which is inherently unpredictable, and are as well often heterogenous in composition. Common problems encountered in working with biologics include difficulties in fully characterizing the biologic using the standard analytical techniques used for small molecules, difficulties in purification, and highly challenging manufacturing protocols, where even slight differences in the manufacturing process can profoundly alter the activity of the biologic. Thus, the development and commercialization of a biologic can be expected to be highly challenging, painstakingly slow, and ultimately much higher risk than that of small molecule drugs.

The statistics of biologic drug development to date bears out these expected risks. The cost of a biologic product’s development can range from \$800,000 to \$1.2 billion. The development timeline takes between twelve to fifteen years, from initial research through FDA approval. Production costs can range from \$250-\$450 million for a biologic’s cell culture facility and it takes three to five years to construct such a facility before the drug enters the clinical setting. Manufacturing expertise is also an issue: manufacturing of biologics typically requires 250 or more critical tests, in contrast to the 40-50 critical tests typically required for small molecule drugs. In addition, only 20% of biologics entering clinical trials receive approval, as there are many late-stage failures. Further, of those biologics approved, only 34% earn profits equal to or greater than the actual development costs. With these considerable barriers to entry in mind, few companies are willing to or capable of, entering the biologics market. Because of these difficulties, biologic drugs are also very expensive – increasing the pressure for a regulatory scheme which will increase competition and lower costs. Any such scheme, however, must carefully balance the high barrier to entry for innovators against these cost considerations if innovation, and the flow of new biologic drugs into the market, is to continue.

Current Regulatory Framework for Biologics

The FDA traditionally approves new drugs under Section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)⁴, while approval to market a biologic is granted by issuance of a license governed under Section

351 of the Public Health Services Act (PHS Act)⁵. In the past, however, the FDA has used the FD&C Act to approve some biosimilars, including human growth hormone. As these terms are used by the FDA, the “biosimilar” is an inexact copy of an original, brand name biologic (the “reference”) with no clinically meaningful differences, and has a molecular structure and mechanism of action highly similar to the reference.

There is currently no framework specific for abbreviated regulatory approval of biosimilars in the U.S. The only existing regulatory mechanism in practice for abbreviated regulatory approval of pharmaceutical products in the U.S. is the Hatch-Waxman Act. The Hatch-Waxman Act, codified in the FD&C Act, provided an abbreviated process for regulatory approval of generic small molecule drugs. The act was intended to strike a balance between the interests of innovators who conducted research leading to approval of new, brand name drugs and the interests of generics manufacturers that make products equivalent to the innovators’ and market such products at reduced prices. The Hatch-Waxman Act sets forth the mechanism for abbreviated new drug applications (ANDAs) by requiring demonstration of bioequivalence, without additional clinical safety or efficacy testing. Chemical identity of the small molecule drug is required, with the active ingredient of the generic being the same as that of the already-approved brand name drug. The route of administration, dosage form, strength, and proposed labeling must be the same as the brand name drug. The Hatch-Waxman Act provides patent term extension of up to five years for the innovator, and also five years of data exclusivity, which prevents the generic competitor from relying on the innovator’s data on research and clinical trials when applying for approval of generic small molecule drugs. The act also requires a listing of patents covering approved drugs in the Approved Drug Products with Therapeutic Equivalence Evaluations, known as the Orange Book. In addition, the act has a pre-approval patent dispute resolution process.

While there is no process for abbreviated regulatory approval of biosimilars in the U.S., Europe has established such a process, through the European Medicines Agency (EMA) for biologics. The EMA established the “Similar Biological Medicinal Products” guideline in 2004 for approval of biosimilars. The active substance in the biosimilars must be similar in both molecular and biological terms to the active substance of the reference biologics. The form, strength, and route of administration should also be the same as the reference product. Normally, pre-clinical tests

and clinical data will be required for biosimilars. The EMA also provides ten years of data exclusivity for the reference biologics, which may be extended to eleven years for new indications of approved biologics. Biosimilars approved by the EMA must undergo post-marketing monitoring. To date, some of the EMA-approved applications for biosimilars include those for Epoetin alfa, Binocrit, Valtropin, Abseamed, and Filgrastim Hexal.

Key Issues in the Proposed Legislation

It has long been recognized that the U.S. is in need of a formal regulatory pathway for biosimilars, to complement the abbreviated approval process for generic small molecules under the Hatch-Waxman Act. Current proposed biosimilars legislation to amend the PHS Act include H.R. 1427 (“Promoting Innovation and Access to Life-Saving Medicine Act”) introduced by Representative Waxman (D-CA)⁶, and H.R. 1548 (“Pathway for Biosimilars Act”) introduced by Representative Eshoo (D-CA)⁷. In addition, there is the Hatch/Enzi amendment that was approved as part of the Affordable Health Choices Act by the Senate Health, Education, Labor and Pensions (HELP) Committee on July 13, 2009 and is patterned after the 2007 HELP Committee compromise, S. 1695 (“Biologics Price Competition and Innovation Act of 2007”). Table 1 below details the proposed legislation for biosimilars:

Some of the key issues for any proposed biosimilars regulatory pathway are the same as those addressed in the Hatch-Waxman Act for generic small molecule drugs. These issues include patent term extension, the term for data exclusivity, clinical trial requirements,⁸ how patent law applies to biosimilars, patent listing requirements,⁹ and confidentiality of reference data (i.e., the reference biologic company’s data). Some of these issues are addressed below:

1. Patent Term Extension

When the General Agreement on Tariffs and Trade (GATT) was signed into law in 1994, the term of a patent under U.S. patent law shifted to twenty years from the earliest date of filing. The Hatch-Waxman Act’s provision on patent term extension allows up to five additional years for patents on drugs subject to regulation under the FD&C Act. This restores a portion of the patent term during which the innovator was unable to sell a product while awaiting FDA approval. This patent term extension is subject to a fourteen-year cap of post-approval patent term. On average,

Table 1: Comparison of the proposed pieces of legislation for biosimilars approval

	Waxman (H.R. 1427)	Eshoo/Inslee (H.R. 1548)	Hatch/Enzi Amendment & S. 1695
Data Exclusivity	5 years reference 3 years modification 6 mos. new indication	12 years reference 2 yrs new indication 6 mos. pediatric	12 years
Clinical Studies	FDA discretion on clinical or other safety studies	Immunogenicity studies required unless FDA published guidance w/data	Clinical trials regarding effectiveness required
Patent Listing	On request	No Orange Book equivalent. On request after reference biologic company receives application	On request after reference biologic company receives application
Confidentiality of Exchanged Info for Dispute Resolution	Not addressed	Confidential	Confidential
Time Limits	Not addressed	Application may not be submitted until 4 years after reference product's license date	Application may not be submitted until 4 years after reference product's license date
Patent Term Extension	Not addressed	Not addressed	Not addressed
Labeling	Not addressed	Biosimilar's labeling and packaging must distinguish it from reference product	Not addressed
Reference Data Confidentiality	Not addressed	Not addressed	Not addressed

patent-protected small molecule drugs are marketed for 11.5 years with patent exclusivity, and brand name drugs in the U.S. are marketed for 13.5 years before the entry of generic competition. This issue is not addressed, however, by any of the proposed schemes for biosimilars approval that are presently under consideration. Due to the high costs, and long lead time, for commercialization of biologics – both exceeding that required for commercialization of a small molecule drug – the availability of patent term extension is certain to be a hotly debated issue for companies in this space.

2. Data Exclusivity

Data exclusivity prevents the generic competitor from relying on the reference drug's data on research and clinical trials when applying for approval of generic drugs. When patent law protection is certain and the length of protection is long, as they are for the small molecule drugs, data exclusivity is of lesser importance than when patent protection is uncertain and/or expires at or shortly after market approval of the patented product. Both problems are manifest in the case of biologics. As discussed in section 1 above, none of the

proposed legislation addressed patent term extension. Thus, the length of patent protection for reference biologics is far from certain, and, given the long lead time to develop biologics and to bring them to market, without patent term extension, many of the biologics will be off-patent by, or very shortly after, they reach the market. Indeed, many currently-marketed biologics will go off-patent beginning this year, with approximately \$25 billion worth of biologics losing patent protection by 2016. In addition, the strength of patent protection for biologics is also uncertain, as discussed in more detail below at section 3, *infra*. Because of the uncertainty in patent-term extensions, the question of data exclusivity for biologics has become a particularly intense area of debate. As summarized in Table 1, the Waxman bill proposes five years, the Eshoo bill proposes twelve years, and the Hatch/Enzi amendment proposes twelve years of data exclusivity for reference biologics. In addition, the White House has proposed seven years for the data exclusivity period, which it deems as “generous.” Currently, Congress appears to favor the twelve years of data exclusivity¹⁰.

3. Reference Biologics Patents and Biosimilars

In contrast to generics for small molecule drugs, biosimilars do not have to be exactly the same in structure and composition as their reference biologics. Instead, the biologics can be “similar” to the reference drug. Under this “similar standard”, one concern is that a biosimilar will be comparable enough to rely on the reference biologic’s data, but different enough to avoid the reference biologic’s patent protection. Opportunities for design-around may arise, which is typically not a concern for small molecule drugs since the generic and the small molecule must share identical active ingredients. Because the small molecule reference drugs almost always protects its active ingredient by patent, patent law protects the reference drugs from infringement. In contrast, when the copier can enter the market with a “biosimilar”, the reference biologic’s patent may not be sufficient to protect against the biosimilar – as an exact copy of the active ingredient is not required and as set forth below, claims to biologic inventions are often narrowly construed, both literally and under the doctrine of equivalents, thus limiting the range of potential infringing products within the reach of the reference biologic’s patent.

As an example of the challenges presented in using patents to protect against the introduction of biosimilars during the patent term of the innovator biologic, courts have required complete identity in amino acid

sequence for a polypeptide to infringe a patent under literal infringement. See *Hormone Research Found. v. Genentech, Inc.*, 904 F.2d 1558, 1564 (Fed. Cir. 1990) (defendant found not to infringe the patent claim at issue because its product had a one amino acid difference from the claimed sequence). Patentees have fared no better in trying to reach such differences in structure using the doctrine of equivalents. See *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006) (patent claims directed to 166 amino acid EPO protein found not to cover competitor’s 165 amino acid EPO protein under the doctrine of equivalents). As illustrated by these precedents, many biosimilars may be capable of avoiding patents covering reference biologics— hence such issues as confidentiality and data exclusivity are of heightened importance.

4. U.S. Trade Secrets Law and Biologics Manufacturing Data

Yet another area of concern for reference biologic companies is protecting the confidentiality of their manufacturing information and reference data. Again, this is an issue that is of particular interest to biologics as the method for manufacturing a small molecule drug with known chemical structure is generally less affected by process variables. Once the pathway for making a given chemical entity is understood (a process that is generally disclosed in a patent directed to the entity), the manufacture of active chemical by a third party is far easier to achieve than is the case with a biologic. For a reference biologics company, manufacturing data, particularly relating to scale up from lab to commercial quantities, where even such details as tank size can profoundly impact production and activity levels, may be as valuable as the identify of the biologic itself. This information is therefore generally held by companies as a closely-held secret, subject to trade secret protection.

Trade secrets law protections vary by state but generally share the characteristics of requiring that the information be of economic value to the owner, and that reasonable efforts are used to protect the information from public disclosure. This means trade secrets are excluded from patents, which are published and released to the public domain (which also raises potential issues of best mode disclosure, which is beyond the scope of this article and not addressed here). The FDA has historically recognized that each biologic is uniquely linked to its manufacturing process, and has protected such information if provided under an application to the FDA. With respect to continuing this protection under a biosimilars regulatory scheme, the key question will

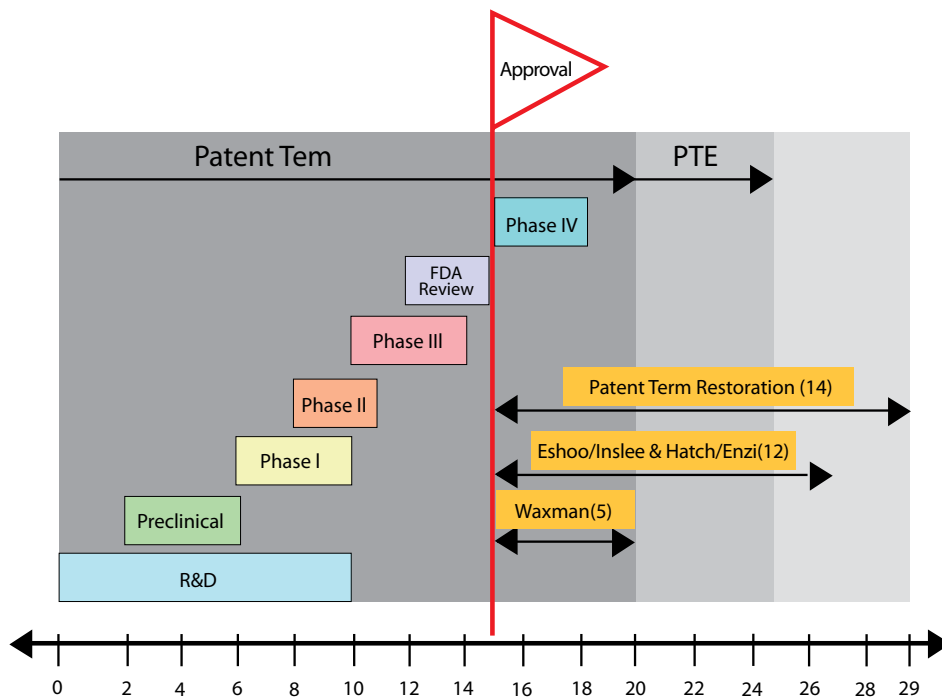


Figure 1: *Timeline for drug development and the innovation conundrum*

be whether the FDA and/or biosimilar manufacturer will be allowed to review the data on the reference biologic’s manufacturing process. As a corollary to the question of access, there is also the question of how any such access would be implemented. For example, will the reference biologic company be able to audit the trade secret protection measures of the biosimilar manufacturers? And how will the scheme reconcile the reference biologics companies’ need to maintain trade secrets and competitor’s need to access data on the reference biologic in order to successfully manufacture the product. None of these questions are addressed by any of the proposed legislations.

5. The Innovation Conundrum

As the Table 1 summary indicates, the current proposed pieces of legislation on biosimilars have not yet addressed significant intellectual property issues of importance to both reference biologics and biosimilar manufacturers. Patent term extension, patent listing requirements, how patent law applies to biosimilars, and confidentiality of reference data remain to be addressed. Due to the high barrier to entry for both the reference biologic company and the biosimilar manufacturer, there is a fundamental dispute as to how data exclusivity should be treated. Longer data exclusivity helps the

reference biologic company recoup its investment in research, development, and FDA approval – but also delays entry of competitors into the marketplace (thus delaying cost savings). Shorter data exclusivity will provide consumers earlier and possibly cheaper access to biologic drugs by allowing biosimilar companies to compete with lower prices. However, if the data exclusivity period is too short, there will be fewer companies willing to invest in developing and making the reference biologic drug to begin with. This conundrum is now being decided at the nation’s capital. The length of data exclusivity arrived at in the ultimate abbreviated regulatory scheme for biologics will have significant implications in the life sciences industry for how

investments are made, and what types (and number) of products will be developed in the next decade and beyond.

Figure 1 depicts a typical drug development timeline, and the proposed biosimilars data exclusivity terms in contrast with the Hatch-Waxman Act. If any bill on biosimilars becomes law without provisions on intellectual property issues, amendments may be necessary down the road and resolution of many of these issues will end up at the courts.

Conclusion

Biologics are complex; they are expensive and difficult to develop. They are also difficult to protect by patent both due to the long lead times for introduction into the market (in the absence of adequate patent term extension provisions) and due to the challenges in obtaining claims that will cover biosimilars, also inherently challenging in protecting by patents alone. However, trade secret protection is also challenging in a biosimilar environment. The methods of production, typically protected by trade secrets, are of such critical importance to the final activity and efficacy of these drugs that there is debate as to how to ensure the comparability in safety and efficacy in

follow-on biologics without disclosing the most closely-held trade secrets of the innovator biologic – a result that destroys trade secret protection by the act of its very disclosure. While there is a need to strive for more affordable drugs under healthcare reform, it is important to balance that need with incentives toward innovation, as well as rewarding the lengthy and costly research and development associated with biologics. Due to the unresolved intellectual property issues, companies need to pay close attention to how the biosimilars regulatory approval pathway unfolds in the U.S.,¹¹ and be prepared for resolving legal disputes in the court system.

References

1. Deborah Fishman and Elizabeth Howard are partners in the Intellectual Property Group at the law firm of Orrick, Herrington & Sutcliffe LLP. Both of them work in Orrick's Silicon Valley office in Menlo Park, California. Zheng Liu is a managing associate with the same group at the same office. Tracy Huang was a summer associate in the same group in 2009 and will start as an associate at Orrick in 2012. Please contact Zheng Liu at jenliu@orrick.com for questions.
2. This is the definition used by the Food & Drug Administration ("FDA").
3. FDA defines generic drugs as a drug that is the same as a brand-name drug in dosage, safety, strength, quality, the way it works, the way it is taken, and the way it should be used, but without patent protection for active ingredients. Due to the fact that this definition does not work precisely with generic biologics as biologics by nature are not identical when manufactured by different companies, the industry has generally adopted "follow-on biologics" or "biosimilars." This article uses "biosimilars" as the authors believe it most accurately reflects the nature of the generic version of the biologics drugs.
4. The Drug Price Competition and Patent Term Restoration Act, Pub. L. 98-417, codified in 21 U.S.C. § 355. This act provided the pathway for approval of abbreviated new drug applications (ANDAs).
5. The PHS Act can be found at: <http://www.fda.gov/RegulatoryInformation/Legislation/ucm148717.htm>.
6. Rep. Waxman's proposed legislation can be found at: <http://www.govtrack.us/congress/bill.xpd?bill=h111-1427>. There is an identical bill in the Senate, S. 726, introduced by Senator Schumer (D-NY).
7. Rep. Eshoo's proposed legislation can be found at: <http://www.govtrack.us/congress/bill.xpd?bill=h111-1548>.
8. Hatch Waxman Act does not require clinical trial of generic small molecule drugs once its identity to reference drugs are shown. Due to the fact that biosimilars are not exact copies of reference biologics, all the proposals include some level of clinical trial requirements. There appears to be no debate on the need of clinical trials (EMA also requires clinical studies), there is differences in opinions on exactly what should be required. This issue is not closely related to intellectual property protection thus not discussed further in this article.
9. Hatch Waxman Act requires reference small molecule drug companies to list patents that cover these drugs. This is commonly referred as "Orange book listing." The proposed legislations do not have such requirement, but both Eshoo/Inslee and Hatch/Enzi proposals provide that reference biologic company to provide such information to biosimilar company after receiving a biosimilar application. This issue is not hotly contested and thus the authors will not discuss this issue in further detail.
10. On November 7, 2009, the House passed the Affordable Health Care for America Act (H.R. 3962) in which the twelve-year exclusivity period of the Hatch/Enzi amendment (adopted by the Senate HELP Committee in July 2009) is incorporated.
11. It is worthwhile noting that currently there is no formal regulatory framework for biosimilars in China or India, yet these two countries are seen as the markets with highest potential for biosimilars penetration. While the lack of a regulatory mechanism has slowed the development the U.S. biosimilars market, companies in China and India do not appear to face the same barriers to market entry. The biosimilars industry has launched many products in Asia's emerging markets. Marketed biosimilars in China include human growth hormone, insulin, EPO, IL-2, interferon, and vaccines. Biosimilars in China accounted for more than 90% of the \$3 billion biopharmaceutical market in 2007. Lastly, some of the world's most active and leading companies in the biosimilars industry come from China and India: 3SBio, Interlong, Bharat Biotech, Dr. Reddy's, Emcure Pharmaceuticals, and Ranbaxy.