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THE PHARMACEUTICAL FRONTIER:
EXTENDING GENERIC POSSIBILITIES TO
BIOLOGIC THERAPIES IN THE BIOLOGICS
PRICE COMPETITION AND INNOVATION ACT
OF 2007

I. INTRODUCTION

The modern generic drug industry is generally thought to have been borne out of The Drug Price Competition and Patent Term Restoration Act of 1984 (universally known as the Hatch-Waxman Act). This legislation authorized the Federal Food and Drug Administration (FDA) to approve generic drugs upon the manufacturer’s submission of proof of bioequivalence. Prior to the Hatch-Waxman Act, in order to obtain FDA approval, manufacturers of generic drugs were required to conduct the same clinical tests as manufacturers of new, brand-name drugs. The rigorous requirements for FDA approval narrowed the generic

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2. Generic drugs are drugs made to the same chemical formula as an existing, FDA-approved, brand-name compound.
3. The FDA defines bioequivalence as “pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.” Generally, this is determined by looking at pharmacokinetic parameters such as the area under the curve, AUC(0 - ¥), Cmax, tmax, t1/2 and k of the therapeutic moiety. See 21 CFR § 320.1 (2007).
4. A manufacturer of a new drug can file an application for FDA approval after completion of required clinical trials, if the data support the safety and effectiveness of the compound. These applications typically are 100,000 pages or longer and include all the data gathered during development and in clinical testing. The FDA is legally allowed six months for review of the application, however, the average new drug application takes 30 months for review. See generally 21 C.F.R. § 312 (2007).
drug manufacturer’s profit margin and stifled their growth, inhibiting consumer access to affordable medicine. Thus, the Hatch-Waxman Act marked the dawn of the generic drug era as we know it.

After the passage of the Hatch-Waxman Act, the generic drug industry grew tremendously in response to an increased demand for lower-cost pharmaceuticals. The Hatch-Waxman Act spurred the generic drug industry’s growth, in part, by an expedited approval procedure for "small-molecule chemical compounds." However, what worked under the Hatch-Waxman Act for these compounds is not a complete answer to the current problem of high-cost medication. The FDA expedited approval procedure under Hatch-Waxman excludes all recombinant protein or "biologic" drugs.

To remedy what the Senate perceives as a shortcoming in the FDA expedited procedure, the Senate is currently considering the Biologics Price Competition and Innovation Act of 2007 (Biologics Act). The Biologics Act is sponsored by Democrat Senator Edward Kennedy of Massachusetts. Passage of this act would essentially extend many of the provisions of the 1984 Hatch-Waxman Act to biologic drugs. This, in turn, would likely promote development of lower-cost alternatives to increasingly important biologic therapies. Furthermore, it could stimulate growth in the generic drug industry comparable to that experienced by small-molecule drug competitors after the passage of the Hatch-Waxman Act.

Due to the differences between small-molecule and biologic compounds, however, a number of problems arise when the Hatch-Waxman provisions, which were originally developed for small-molecule compounds, are applied to biologics. Specifically, biologic compounds are larger and more complex than small-

6. See infra notes 53-56 and accompanying text for a definition of "small molecule chemical compounds" and a discussion of their properties.
7. See infra note 37 and accompanying text for a definition of "biologic" drugs.
8. For an extended discussion of the similarities of the provisions in the Biologics Act to those of the Hatch-Waxman Act, see infra Section II.
molecule compounds. They are also synthesized by processes that attempt to mimic in vitro biological production,9 in contrast to the traditional combinatorial chemistry techniques used in laboratory synthesis of small-molecule drugs.10 Due to the differences in the synthesis procedure, inconsequential changes in the manufacture of small-molecule compounds could all have serious health consequences if occurring in biologic production.11

Aside from the health concerns associated with "generic biologics,"12 there are a number of concerns about what the impact of biologic legislation will be on United States patent law. First, if it is impossible to synthesize an identical compound, the effect could be to preclude patentability on the grounds of "enablement."13 The patent-holders, here manufacturers of brand-name drugs, should be prohibited from simultaneously arguing that their patented compounds are impossible to replicate and that they

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9. In vitro production, or synthesis within the living organism by its own processes, is often mimicked in a laboratory setting using cloning techniques and cell-line development.

10. Most small-molecule chemical compounds are not synthesized naturally in vivo, unlike most biologics (for example, human growth hormone, a biologic, is produced naturally in the anterior pituitary gland, while aspirin, a small-molecule chemical compound, must be made outside the body). Development and production of small-molecule compounds, then, are possible using mainstream combinatorial chemistry techniques (e.g. high throughput screening, cell-based assays, reaction-based chemistry), while biologic production requires more sophisticated techniques.


are enabled.\textsuperscript{14} Second, patentability is at issue because many biologics are compounds already produced \textit{in vivo}, such as insulin or human growth hormone. While the methods of synthesis for this type of drug are complex and could potentially be novel, the biologic itself might not meet the patentability requirement of novelty.\textsuperscript{15} These issues should be considered by legislators before assuming that the provisions of the 1984 Hatch-Waxman Act will prove as successful for biosimilars as they did for small-molecule compounds in the 1980s.

This is not to say that the Hatch-Waxman Act is entirely without merit when applied to biologics. While the concepts of the Hatch-Waxman Act need complements in the biologic drug industry, the nature of the differences between the drugs developed in the 1980s and the drugs being developed today merit a closer look before we can assume that the Biologics Act will procedure results similar to the Hatch-Waxman Act.

Section II of this article provides a background of the issues facing generic pharmaceuticals with the emergence of biologic therapies. This section surveys the past attempts to regulate the biologic industry. It also provides an overview of the special circumstances facing biologics. Section III analyzes the legislation proposed to ameliorate the problems in the approval process of biologics. Finally, Section IV examines the likely effects of the Biologics Act on the interested parties. This section also examines how the Biologics Act relates to existing tenets of our patent law.

\section*{II. BACKGROUND}

Any discussion of how to fix generic pharmaceutical approval must begin with a discussion of the flaws in our current system. To that end, Part A of this section provides an overview of the ubiquity of generic drug use and the incumbent financial issues

\begin{itemize}
\item \textsuperscript{14} See infra Section IV.
\item \textsuperscript{15} The requirement that an invention be novel in order to qualify for a patent is found in 35 U.S.C. \textsection 102 (2006). Other patentability requirements include that the invention be useful, 35 U.S.C. \textsection 101, that it be nonobvious, 35 U.S.C. \textsection 103, and that it be enabled, have an adequate written description in the specification, and disclose the best “mode” of making or using the invention, 35 U.S.C. \textsection 112.
\end{itemize}
surrounding it. Part B discusses the Hatch-Waxman Act, the solutions it provided, and the effect of those solutions on the pharmaceutical industry. Part C introduces biologic drugs and discusses why they have been excluded from the current system of FDA approval.

A. A Generic Problem

To the average consumer looking at the shelf in the drugstore, the differences between Advil and Walgreen's ibuprofen tablets are probably not apparent or significant. Noticeable differences may be limited to the price tag and the trademarks. Consumers have increasingly become accustomed to having a choice between either a generic or a brand-name drug over the past three decades. Generic alternatives are now a familiar and expected option in drugstores, pharmacies, doctor's offices, and hospitals now that generic pharmaceutical companies have sprung up to meet the overwhelming need for lower-cost medication.

This need for lower-cost alternatives to brand-name drugs has only grown in the nearly 25 years since Congress last considered generic drugs. Indeed, skyrocketing pharmaceutical costs and increased consumer demand have focused increasing attention on generic drugs as a possible solution to the rising costs of healthcare. As Senator Orrin Hatch of Utah recently noted while discussing the future of generics:

A February report by the Center for Medicare and Medicaid Services paints the picture very well: America's health care spending in the next ten years will double to $4.1 trillion. Or, to look at it another way, that's 20 cents out of every dollar spent. We spend about $7,500 per capita on health care in the U.S. Yet, in 2016, that will rise to an astounding $12,800 per person. Greater spending for pharmaceuticals is expected to fuel much of the

16. Per capita refers to the amount spent per unit of the population: by or for each person.
With such large a percentage of national spending tied to healthcare, 47 million uninsured Americans in 2006 and another 38.3 million covered by Medicaid alone, the price of medication is a critical issue for citizens and legislators alike. Prices are not an isolated issue. Prices are inexorably linked to healthcare, monetary and fiscal policy, management of the national debt, and, ultimately, overall standard of living.

Drug prices are also an especially “hot-button” issue because of the looming healthcare crisis in America. As the Congressional Budget Office has stated:

Growth in health care spending has outstripped economic growth regardless of the source of its funding . . . . The major factor associated with that growth has been the development and increasing use of new medical technology . . . . In the health care field, unlike in many sectors of the economy, technological advances have generally raised costs rather than lowered them.

This increase in inefficient spending, coupled with the unraveling of employer-based healthcare plans and the rise of Medicaid, contributes to a growing sense of panic about the future of American healthcare. With the aging of the large “Baby Boomer” generation and the incumbent increase in the cost of their healthcare and medication, the public has finally realized that there is a problem. Candidates for the 2008 presidential election have capitalized on this fear. Nearly every debate included questions

17. Hatch Address, supra note 12.
20. Id.
21. Id.
about plans for stemming the tide of runaway healthcare costs. For politicians, it is largely a self-preservation mechanism — the staggering rate of growth of the percentage of the gross domestic product (GDP) taken up by entitlement programs, such as Medicaid, contributes heavily to the national debt and decreases funds for federal spending.\textsuperscript{22} The rapid and seemingly unstoppable rise in healthcare spending has created a looming crisis for citizens, drug companies, healthcare providers, and politicians.

Generic alternatives have made an immense impression on the pharmaceutical industry. In 1994, (ten years after the Hatch-Waxman Act was passed), consumers of generic drugs saved between $8 and $10 billion in retail pharmacies alone on prescription drugs by purchasing generic drugs instead of brand-name drugs.\textsuperscript{23}

Though the financial impact on consumers has been significant, the impact on research and development in the pharmaceutical sector has been equally momentous. A report by the Congressional Budget Office stated, "[b]etween 1983 and 1995, investment in [research and development] as a percentage of pharmaceutical sales by brand-name drug companies increased from 14.7 percent to 19.4 percent. Over the same period, U.S. pharmaceutical sales by those companies rose from $17 billion to $57 billion."\textsuperscript{24} Clearly, the introduction of generics into the marketplace has not stifled research and development efforts by companies marketing primarily brand-name drugs.

\textit{B. Take 1: The Hatch-Waxman Act of 1984}

The Hatch-Waxman Act of 1984\textsuperscript{25} was enacted to balance the competing interests of parties affected by the introduction of generic drugs onto the consumer market. In order to compete with

\begin{footnotesize}
\begin{enumerate}
\item Id.
\item Id. at xv.
\end{enumerate}
\end{footnotesize}
the brand-name drug manufacturers, the new generic pharmaceutical companies needed a relaxed approval process and an avenue for expedited patent litigation. Conversely, existing brand-name pharmaceutical companies needed to maintain their profit margins as an incentive to continue research and development. Finally, the public needed access to safe and affordable medication and a progressive drug market.

As a compromise to these competing interests, the Hatch-Waxman Act specifically authorizes "Abbreviated New Drug Applications" (ANDAs), which had been under discussion within the FDA as a solution to their rigorous approval requirements.26 ANDAs essentially allow a company that wants to produce a generic version of a patented drug to bypass the FDA's requirements of proving that the drug is safe and effective. So long as the formula is identical to the brand-name drug, an ANDA applicant is only required to submit proof of the bioequivalence of the brand drug with the generic.27 After certain periods of market exclusivity given to the original New Drug Application (NDA) holder,28 a generic company may file an ANDA, which certifies one of four things: (1) Paragraph I certifies that the drug has not been patented; (2) Paragraph II certifies that the patent has expired; (3) Paragraph III certifies the date on which the patent will expire and that the generic will not go on the market until after that date; or (4) Paragraph IV certifies that the patent is not infringed or is invalid.29


28. The manufacturer who requests FDA approval for a brand drug files a New Drug Application and is awarded any "exclusivities" that apply to its application. There are six major exclusivities under current U.S. regulations: new chemical exclusivity, new use or indication exclusivity, new formulation exclusivity, orphan drug exclusivity, pediatric exclusivity, and generic filer exclusivity. These carry different periods of monopoly depending on which are awarded. For a complete discussion, see MARTIN A. VOET, THE GENERIC CHALLENGE: UNDERSTANDING PATENTS, FDA & PHARMACEUTICAL LIFE-CYCLE MANAGEMENT, 57-65 (2005).

29. Mossinghoff, supra note 27, at 189.
A party filing an ANDA under Paragraph IV must give notice to the patent holder that it has filed an ANDA. The filing is considered an act of literal patent infringement for enforcement purposes. The patent-holder then has forty-five days to file suit for infringement. During this forty-five day period, the ANDA’s approval is suspended. If the patent holder chooses to file suit, the ANDA will not be processed for another thirty months. This allows both parties to litigate the Paragraph IV allegation. The notice requirement and thirty-month stay of approval, coupled with patent term extensions and market exclusivity provisions awarded in some circumstances, make the Hatch-Waxman Act attractive for brand-name drug manufacturers. However, if the generic company prevails and can show noninfringement or invalidity of the patent under Paragraph IV, it is awarded 180 days of market exclusivity for the generic version of the drug. This provision makes ANDAs attractive to generic companies as well.

Before reaching its current form, several provisions of the Hatch-Waxman Act had been modified by the Medicare Act of 2003. The two most notable alterations included: (1) requiring brand-name manufacturers to sue within forty-five days or else forego later suit, thus precluding manufacturers from waiting for damages to accrue because generic manufacturers had begun marketing; and (2) codifying Mova Pharmaceuticals, which held that a district court decision does not trigger the 180-day exclusivity for the generic manufacturer until an appeal has been taken.

30. As opposed to infringement under the doctrine of equivalents, which “allows a finding of patent infringement even when the accused product does not fall within the literal terms of the claims.” TrafFix Devices, Inc. v. Mktg. Displays, Inc., 532 U.S. 23, 31 (2001).
32. Bristol-Myers Squibb Co. v. Royce Labs., 69 F.3d 1130, 1132 (Fed. Cir. 1995).
34. See CONGRESSIONAL BUDGET OFFICE, supra note 23, at xiv.
35. Id.
denied or waived.\(^{38}\) Prior to passage of the Medicare Act of 2003, a prevailing generic manufacturer would have to choose between risking the loss of the exclusivity allowed under Hatch-Waxman and risking the possibility that the noninfringement or invalidity ruling would be overturned on appeal. The latter possibility could result in treble damages against the manufacturer for its intervening acts of infringement.\(^{39}\)

The procedure for generic drug approval mapped out in the Hatch-Waxman Act has since become the standard method of operation for generic drug manufacturers. It has also succeeded in furthering the public’s interest in timely access to lower-cost generic drugs after the expiration of the brand-name drugs’ patents.\(^{40}\) The six-month exclusivity awarded to the first successful Paragraph IV filer, however, has delayed the low cost access to generic drugs. The period of exclusivity allows generic marketers to charge initial prices almost as high as the brand-name drugs and creates tremendous profit potential.\(^{41}\) By narrowing the field to only two competitors, namely the brand-name drug manufacturer and one generic manufacturer, the generic manufacturer can easily keep its price just below that of the brand-name drug manufacturer, who is trying to recoup the high research and development costs associated with pharmaceutical development.\(^{42}\) Though generic manufacturers incur litigation costs, cost of a legal advisory opinion,\(^{43}\) additional development

\(^{38}\) Amphastar Pharm., Pre-Effective Amendment to Registration Statement (Form S-1/A), at 53-54 (May 13, 2005).


\(^{40}\) See supra note 5 and accompanying text.


\(^{42}\) Estimates of the cost of developing a new molecular entity (novel drug) run the gamut from $800 million to $2 billion per drug. Economists estimate that only thirty percent of the compounds developed will actually make money for the developer. However, continued investor confidence in the industry enables large-scale research and development to continue apace. Neal Masia, The Cost of Developing a New Drug, in FOCUS ON INTELLECTUAL PROPERTY RIGHTS (2006), http://usinfo.state.gov/products/pubs/intelprp/cost.htm.

\(^{43}\) Generally before filing a Paragraph IV ANDA, a generic manufacturer will request an advisory opinion from outside counsel regarding infringement and validity of any patents covering the compound, method of manufacture or synthesis, or use.
costs, and filing costs associated with an ANDA, they have few expenses compared to brand-name manufacturers.

Barr Pharmaceuticals,44 for example, recently filed a Paragraph IV ANDA covering Prozac and successfully invalidated Eli Lilly’s patents covering the compound. In the six-month period of exclusivity alone, sales of the generic drug reached $311 million.45 This kind of profit is a powerful incentive for litigation under the Hatch-Waxman Act, and the incentive has worked. The litigation costs are not a powerful enough deterrent to make generic pharmaceutical companies think twice about using the reexamination procedures. As a result, a flood of ANDA litigation has ensued.46

C. Biologics—the “Black Sheep” of the Hatch-Waxman Family

Despite challenges to the Hatch-Waxman Act, it has expedited approval of generic drugs, significantly lowering costs for the consumer. The Act, however, applies only to medications classified as small-molecule chemical compounds.47 The Hatch-Waxman Act does not cover recombinant protein drugs, also

44. Barr Pharmaceuticals, Inc. is a global specialty pharmaceutical company operating in more than thirty countries worldwide. Along with their subsidiaries, Barr Laboratories, Duramed Pharmaceuticals, and PLIVA, they develop, market, and manufacture generic and proprietary drugs, biopharmaceuticals, and active pharmaceutical ingredients. They currently market more than 120 generic and 25 proprietary drugs in the U.S., and more than 550 products worldwide. Barr Pharmaceuticals, Inc., http://www.barrlabs.com (last visited Apr. 28, 2008).

45. Masia, supra note 42.

46. See The Generic Drug Maze: Speeding Access to Affordable, Life Saving Drugs: Hearing Before the S. Spec. Comm. On Aging, 109th Cong. (2006) (statement of Gary Buehler, Director, Office of Generic Drugs, Food and Drug Administration). In 2000, the FDA received 335 ANDAs and approved 294 of them. Five years later, in 2005, the number of submissions had grown to 766, with only 467 approvals. Id.

47. In 1984, at the time the Hatch-Waxman Act was passed, only one biopharmaceutical drug had been approved for use. Recombinant human insulin was marketed by Eli Lilly starting in 1982 under the brand name Humulin. The biotechnological processes required to synthesize biologics were still being developed at that time, and so legislators naturally focused their efforts towards small-molecule treatments only for the Hatch-Waxman Act.
known as biologics. Biologics are an increasingly important group of therapeutic compounds, but they have no avenue for approval of generic alternatives in the United States.

Biologics are drugs that are created using biotechnological processes that simulate biological molecules (e.g. insulin, human growth hormone, interferon, erythropoietin, vaccines). Biologics are, generally, significantly larger and more complex molecules than traditional pharmaceuticals.\(^{48}\) For example, they cannot easily survive the acidic conditions of the stomach or pass through the lining of the intestine and into the bloodstream. As a result, they are usually injected directly into the bloodstream.\(^ {49}\) Also, due to the size of these compounds, the immune system occasionally attacks biologics present in the bloodstream, leading to undesirable side effects.\(^ {50}\) For example, when Johnson & Johnson changed their manufacturing process for a new anemia drug, the new formulation unexpectedly caused certain compounds to leach out of the uncoated rubber stoppers used in drug storage. This caused clumps to form in the bloodstream and triggered an extreme form of anemia — the very disease that the drug was designed to treat.\(^ {51}\) Antibody-induced pure red cell aplasia was also a concern in European testing guidelines for erythropoietin biosimilars.\(^ {52}\)

Biologic compounds differ from small-molecule compounds in three significant ways. First, their physical characteristics are markedly different. Small-molecule drugs may be composed of dozens of atoms, and their size or molecular weight may be measured in hundreds of daltons.\(^ {53}\) They can be described by a

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49. In contrast, small-molecule compounds are usually delivered via oral dosage.


52. Andrzej Wiecek & Ashraf Mikhail, *European Regulatory Guidelines for Biosimilars*, 21 NEPHROLOGY DIALYSIS TRANSPLANTATION v17, v19 (Supp. 5 2006); see also Michele Kessler et al., *Immunogenicity of Biopharmaceuticals*, 21 NEPHROLOGY DIALYSIS TRANSPLANTATION v9, v10 (Supp. 5 2006).

53. A “dalton” is the standard name given to an atomic mass unit in biochemistry or molecular biology literature. One dalton equals \(\frac{1}{N_A}\) grams,
fixed chemical formula, and, thus, can be chemically synthesized in a lab. Their mechanism of action is usually understood, since they are ordinarily developed with a specific target and function in mind. Biologics, by contrast, are often composed of millions of atoms which can weigh hundreds of kilodaltons. They typically cannot be described by a single chemical formula. As a result, they must be synthesized by organisms such as bacteria or a cell culture. Their mechanism of action is usually imperfectly understood.\textsuperscript{54}

Second, the process of manufacture differs tremendously between small-molecule compounds and biologics. The starting materials for small-molecule drug synthesis are chemicals. Biologics, in contrast, are usually begun with either a DNA plasmid vector\textsuperscript{55} and cells, which mimics \textit{in vitro} production, or a whole animal. The vessel for the synthesis of small-molecule drugs is a specialized glass or metal container; for biologics it is a cell line or a whole animal. Synthesis of biologics can require hundreds of specific isolation and purification steps.\textsuperscript{56} An exact copy is therefore impossible, since changes to the compound itself occur unexpectedly during the process. As professors Roger and Mikhail observe, "side chains can be added, the product can have alterations to its tertiary or quarternary structure through protein misfolding; degradation by oxidation or deamidation can also occur."\textsuperscript{57} These problems are not exclusive to laboratory simulation of the body's production of the compound. The same

\footnotesize{where \(N_A\) is equal to Avogadro's number.}

\textsuperscript{54} The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary, 108th Cong. (2004) (statement of Dr. William Hancock, Chair of Bioanalytical Chemistry, Northeastern University) [hereinafter Hancock Testimony].

\textsuperscript{55} Plasmid vectors are small, circular molecules of double-stranded DNA. A piece of DNA can be inserted through use of a restriction endonuclease and introduced into a host cell that will express the inserted DNA in the form of a desired trait.


\textsuperscript{57} Roger & Mikhail, supra note 56, at 406.
problems occur frequently \textit{in vivo} as well. Human cells, however, have developed a proofreading mechanism that reviews each synthesized protein and can usually remove the "mistakes" before serious problems occur.\cite{58}

Third, manufacturing biologics can pose several problems, including: (1) the nature of manufacture; (2) the unlikelihood that a generic manufacturer could successfully reverse engineer the exact steps of synthesis used by the brand manufacturer; (3) the complexity and size of the molecules; (4) the possibility for serious and unpredictable side effects with even a small change; and (5) the difficulty of quality control, for even a meticulous replication of a biological compound is not identical to the developed compound it attempts to mimic.\cite{59} Such drugs are thus termed "biosimilar," since similarity to the biological molecule is all that can realistically be claimed.\cite{60} Senator Hatch reiterated the distinction in his remarks to the U.S. Chamber of Commerce, when he said, "[t]he concept of bioequivalence simply cannot be introduced into this debate . . . . Instead, we must work carefully to define biosimilarity."\cite{61}

\section*{III. Proposed Legislation: The Biologics Price Competition and Innovation Act of 2007}

\subsection*{A. Finding a place for Biotechnology — the Need for Legislative Reform}

At the Biosimilars 2007 Conference on September 24, 2007, Representative Henry Waxman remarked:

Biotech drugs are the future of medicine. There are

\begin{itemize}
  \item \textit{58.} \textit{Id.}
  \item \textit{59.} \textit{See} Hancock Testimony, \textit{supra} note 54.
  \item \textit{60.} Without the same cell line, (and sometimes even with the same cell line) the nature of biological processes dictates that the products will not be identical. Until stem cell technology provides a workable alternative to the current manufacturing processes (cloning and recombinant DNA technology), similarity, not equivalence, is all that can be claimed. \textit{See id.}
  \item \textit{61.} Hatch Address, \textit{supra} note 12.
\end{itemize}
close to 500 biotech drugs currently in development for a host of serious diseases. In 2006, U.S. biotech sales grew by 20% to $40.3 billion. By way of comparison, this 20% growth in biotech sales is far greater than the 8% sales growth experienced by traditional pharmaceuticals.\(^\text{62}\)

With therapeutic biotechnology becoming an ever-growing field, the market demands a lower-cost alternative to biologic therapies.\(^\text{63}\) Unfortunately, there is no approval process for production of these alternatives under existing U.S. law. Congress has realized as much, and it is currently addressing this problem through the Biologics Act of 2007.\(^\text{64}\) As the Biologics Act stands in the Senate, it will amend the Public Health Service Act\(^\text{65}\) to allow applications for licensure of biological products based on their similarity to already-licensed products.

Currently, most new biologics are not regulated as new drugs under the Food, Drug, and Cosmetic Act. Instead, they are regulated under the Public Health Service Act. Therefore, instead of filing a new drug application (NDA), an applicant must file a biologics application (BLA). A BLA certifies that the product is safe and pure, and that the manufacturing facility is designed to ensure those characteristics.\(^\text{66}\) An applicant, however, may not currently file a BLA for a biosimilar.

To complicate matters, some of the smaller, less complex biologics (such as insulin and human growth hormone) have received initial approval for manufacture via an NDA. As such, these biologics are eligible for generic approval through an ANDA. There is, however, no clear line between those biologics that qualify for an NDA and those that do not. No bright-line size, weight, or complexity standards exist to guide manufacturers in

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63. Id. at 2.
the decision of whether to file an NDA or a BLA application. William Schultz, speaking for theGeneric Pharmaceutical Association, noted:

It is true that today the FDA regulates most biopharmaceuticals under the Public Health Service Act, which, as previously discussed, is not part of the Hatch-Waxman regime. But the Public Health Service Act has for many years contained a provision stating that nothing in that Act shall affect the FDA’s jurisdiction under the FDCA, and it is clear that FDA could regulate all biopharmaceuticals under the FDCA, as it had chosen to do for insulin and human growth hormone. 67

That said, the FDA has been reticent to do so. The Biologics Act was impelled not only by the need to clarify some of these issues but also in response to the district court decision in Sandoz, Inc. v. Leavitt. 68 In Sandoz, Inc., the district court for the District of Columbia directed the FDA to refrain from further delay in deciding whether to approve the license of Omnitrope. 69 Omnitrope, a human growth hormone biologic, was a candidate for approval via a BLA, but the court attempted to put pressure on the FDA to deal with the growing confusion by ordering the agency to respond to the NDA. The agency granted the approval but appealed the decision to the Federal Circuit. It also asserted that it was approving Omnitrope as a “follow-on protein product,” not as a biologic. 70 The FDA emphasized that this did not provide a guaranteed pathway for approval of other

69. Id. at 41.
biosimilars.71

A prompt legislative response is crucial to clarify the FDA’s role and responsibilities in the approval process and prevent continued monopolies, as patents covering the first generation of biologic therapies are beginning to expire. An estimated $28 billion worth of biologic drugs are expected to come off patent by 2015.72 With no pathway for generic approval, the effect will be to grant a perpetual monopoly for the brand-name biologic manufacturer. Such a result would undermine the purpose of U.S. patent law, which is to grant manufacturers only limited monopolies.

The Biologics Act is accompanied in the House of Representatives by the Access to Lifesaving Medicine Act of 2007 (H.R. 1038), which is sponsored by Democrat Representative Henry Waxman of California. It has since been referred to the House Subcommittee on Health and the House Judiciary Committee.73

The Senate bill of the Biologics Act was introduced on June 26, 2007. Since then it has been cleared by the Committee on Health, Education, Labor, and Pensions (HELP) and slated for a vote in the Senate.74 The Biologics Act requires FDA approval of a biosimilar if the applicant can demonstrate the interchangeability of the compound with its brand-name counterpart. Interchangeability can be shown if: (1) the biosimilar “can be expected to produce the same clinical result as the reference product in any given patient”; and (2) the risk in terms of safety or diminished efficacy of alternating between the products is not greater than the risk of using the original (or “reference product”) without switching.75

71. Id.


75. S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed amendment of 42
Despite the route an applicant has chosen to prove interchangeability, the applicant must submit the following with his application:

(1) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
(2) animal studies; and
(3) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency . . . and designed to avoid needlessly duplicative or unethical clinical testing.\textsuperscript{76}

The FDA may waive one or more of these requirements if the applicant presents other supplementary information or if the biologic is comparatively simple. Any finding of interchangeability, however, is prohibited until at least one year after the reference compound is commercially marketed.

In order to be "highly similar" under the first element of interchangeability, the biosimilar must be identical to the brand-name biologic in terms of the route of administration of the biosimilar, the dosage form and strength, the mechanism of action, and the condition for which the product is developed.\textsuperscript{77}

In addition to the simplified requirements for approval outlined above, another difference between the Hatch-Waxman Act of 1984 and the Biologics Act is the length of market exclusivity granted to a new, brand-name (or "innovative") compound. Previously, NDA filers would have to qualify for an exclusivity classification (e.g. Pediatric Exclusivity, New Molecular Entity, Orphan Drug Exclusivity) to gain such market exclusivity.\textsuperscript{78} The Biologics Act provides for an automatic twelve-year exclusivity from the date of approval for any innovative application, in contrast to the five-year exclusivity for new molecular entities under Hatch-Waxman. This

\textsuperscript{76}Id. (proposed amendment of 42 U.S.C. § 262(k)(2)(A)(i)(I) (2006)).
\textsuperscript{77}Id. (proposed amendment of 42 U.S.C. § 262(k)(2)(A)(i)(II)-(IV) (2006)).
\textsuperscript{78}See Krugman & Wells, supra note 19.
longer exclusivity is intended, in part, to offset the higher difficulty level required to perfect the product during research and development.79

The HELP committee approved the bill largely as drafted, although language was added to clarify the sponsors’ intent that innovating products should receive only a single twelve-year exclusivity period from the time of initial approval.80 In reference to the change, Senator Kennedy stated, “We added a provision . . . specifying that this phrase ‘first-licensed’ does not apply to any supplemental application or even a new license for a new indication, route of administration, dosage form or strength.”81 Senator Kennedy’s clarification was in response to the generic community’s concern that a minor and superficial change to the licensed product could entitle the brand-name manufacturer to an additional twelve-year exclusivity — a practice known as “evergreening.”

Many of the other provisions of Hatch-Waxman seem to have simply carried forward into the text of the Biologics Act, though some provisions have slightly different timescales. After filing a biosimilar application, for example, the applicant has 20 days to notify the patent holder.82 Within 60 days of receipt of this notice, the patent holder must issue a list of patents it believes the biosimilar will infringe. The applicant then has 60 days to submit an opinion of invalidity, unenforceability, or noninfringement. After that, the patent holder has 60 days to respond.83 Litigation then takes place if necessary, as under the Hatch-Waxman Act.

Though several prior bills have tangentially addressed the need to extend generic approval to biologic drugs, this is the first to garner significant bipartisan support.84 This is demonstrated by the

79. See Hancock Testimony, supra note 54.
81. Id. (alteration in original).
83. Id. (proposed amendment of 42 U.S.C. § 262(i)(3) (2006)).
84. See, e.g., Access to Life-Saving Medicine Act, H.R. 1038 & S. 623, 110th Cong. (2007); Affordable Biologics for Consumers Act, S. 1505, 110th Cong. (2007); Patient Protection and Innovative Biologic Medicines Act of
three democrats and two republicans who sponsor it. The Biologics Act is also the first bill addressing biosimilars that Senator Orrin Hatch, an architect of the Hatch-Waxman Act, has supported. Senator Hatch stated that he was waiting for a bill that recognized the interests of both generic and novel drug manufacturers.

Despite Hatch’s optimism that the proposed legislation achieves such a balance, not all members of Congress are as sanguine. Senator Sherrod Brown of Ohio drafted an amendment to the bill that would shorten the automatic exclusivity period from twelve to seven years. Senator Brown is likely seeking the support of generic manufacturers who are disinclined to support a proposal that would shorten their opportunity for profit so drastically. A twelve-year exclusivity, however, might decrease the amount of litigation, because it could prove to more profitable to simply wait the additional eight years until the patent expires rather than to engage in costly litigation beforehand. Ultimately, though, Senators Enzi, Clinton, Hatch, and Kennedy were unwilling to reconsider their position, and Brown withdrew the amendment without a vote.

Representative Henry Waxman also had concerns about the length of the exclusivity. He stated:

In the current debate, the industry is calling for 10 or even 14 years of exclusivity. Those periods are so long that they are not only unbalanced, they make the bill a huge give away. Brand companies should receive a reasonable term of exclusivity, but not one that is so long that it would rob the American people of the cost-savings appropriate generic competition brings.

If the Congress ignores the lessons we learned about balance in Hatch-Waxman and passes a bill that puts too much weight on one side of the scale – and replaces adequate incentives with windfall profits – we will lose a huge opportunity.

85. See Hobbs, supra note 80.
86. Waxman Remarks, supra note 62, at 6-7.
Alternatively, two other amendments were also considered. Both amendments would have extended the blanket twelve-year exclusivity by six months. Senator Lamar Alexander of Tennessee proposed the addition of a pediatric exclusivity. Senator Richard Burr of North Carolina proposed an additional six months be given for new indications or uses. Both amendments were ultimately defeated.\(^{87}\)

The twelve-year exclusivity has been the white flag in the tug-of-war contest between generic and brand drug manufacturers and their constituent interest groups. The Generic Pharmaceutical Association calls the twelve years "excessive," while the Biotechnology Industry Organization (BIO)\(^{88}\) insists that fourteen years are necessary to ensure continued innovation.\(^{89}\) Teva Pharmaceuticals, a large manufacturer of many generic drugs, added:

Unfortunately, there are . . . issues that undermine the promise of the bill for consumers, payers and employers who continue to face increasing health care costs. The first issue is the unprecedented twelve years of market exclusivity the bill provides to the innovator company for developing a compound. Teva, as a significant patent holder, supports strong incentives for innovation, however, twelve years of market exclusivity is four years beyond any other nation and seven years beyond the exclusivity period guaranteed for chemical drugs. Our hope is that the Congress will adopt a more constructive and balanced market exclusivity

\(^{87}\) See Hobbs, supra note 80.

\(^{88}\) BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO also produces the BIO International Convention, the world's largest gathering of the biotechnology industry. See BIO, www.bio.org/aboutbio (last visited Apr. 28, 2008).

period that is closer to the Hatch Waxman Act.90

The other proposed bills that have addressed this issue do nothing but add confusion to the debate. For example, while H.R. 1030, the Biologics Act’s House of Representatives’ counterpart, gives no exclusivity at all, H.R. 1956, the Access to Life-Saving Medicine Act, provides for a fourteen-year innovator exclusivity. Since the sponsors of the Biologics Act remain committed to the twelve-year length, however, it seems unlikely that Congress will either extend or shorten it by any significant amount.

Hoping to offset the generic manufacturers’ displeasure with the length of the exclusivity given to innovators, the sponsors also included a one-year exclusivity for the first filer whose application for biosimilar approval (the ANDA equivalent) is granted.91

Senator Kennedy commented that he hoped to attach the Bill to the Prescription Drug User Fee Act reauthorization bill, which was signed into law on September 27, 2007, by President Bush. Unfortunately, the Bill was not ready in time. Nevertheless, the sponsors remain confident in the balance achieved by the drafters. Senator Hatch stated:

Biologics are the future of medicine, and this bill ensures that we will continue to lead the world in biotechnology . . . . We’ve achieved a good balance. We give incentives to continue biological development. We allow generic companies to do what they do best – bring low-cost versions to the market. And we ensure that patients and providers not only have access to low-cost biologics but that they’re also safe.92

Senator Clinton added:

This has real life, real world consequences. As soon as we enact this bill, there are medications for Hepatitis C, multiple sclerosis, cancer and diabetes that will be available for generic versions that will be more affordable for many more people than currently is possible. With this committee’s action today, I am proud that we will both continue the creativity and innovation that is absolutely essential to our pharmaceutical industry and the lifesaving treatments and interventions they are able to provide for us and create a generic path that will begin to lower prices and extend the availability of so many of these treatments to more who need them.\textsuperscript{93}

Despite the hopes of the sponsoring Senators and their confidence in the balance they have achieved, many still have doubts. Representative Waxman, for example, called the chances that any biologics legislation will pass through this congress “extremely slim.”\textsuperscript{94} Many legislators are reluctant to put their name to a bill that might alienate either sector of the pharmaceutical industry, particularly since the industry has been so vocal about its opposition to the Bill.

B. Industry Responses

The debates surrounding the Bill are not limited to the congressional chambers. Generic and brand pharmaceutical manufacturers, along with special interest groups and consumer advocates, are making their opinions known.

The Pharmaceutical Research and Manufacturers of America said in a press release that they “remain concerned that patient safety could be at significant risk if the current legislative follow-on biologics proposals move forward.”\textsuperscript{95} Generic manufacturers

\textsuperscript{93} Id.


\textsuperscript{95} Press Release, Pharmaceutical Research and Manufacturers of America,
responded with confidence in their ability to preserve bioequivalence while ensuring safety. Barr Pharmaceuticals stated:

The science to create affordable generic biotech drugs exists today. . . . It is being done every time a brand manufacturer changes a manufacturing process or location and uses comparability to ensure the biotech drug will provide the same safety and efficacy.

. . . .

. . . [B]iotech firms routinely justify process and site changes via comparability studies. For example, if an innovator biotech company seeks changes in processes supporting the manufacture of their products, or seeks to change the manufacturing location of a product, comparability is the process by which the amended product is judged to provide the same clinical effect and safety profile.96

Speaking for smaller innovative biotechnology companies, Dr. Geoffrey Allan, CEO of Insmed, Inc., stated he believes that safe biosimilars are possible.97 He likened the process of ensuring bioequivalence of biosimilars to the safety checks that are necessary when any biologic manufacturer changes place of manufacture, makes a change in the starting cell line, or changes any step in the manufacturing process.98 If an innovative biologic manufacturer can move production from a plant in the U.K. to a plant in Colorado, as Allan did for Insmed’s IPLEX biologic, all while ensuring that the product maintains the same properties, then it should theoretically be possible to ensure that the properties


98. Id.
remain the same from innovative biologic to biosimilar.99

Some have noted that, ultimately, it may be immaterial whether biosimilars gain an avenue for FDA approval, since it is still the doctors and patients who must be convinced. As one commentator noted, compared to payers and academics, doctors have always been the toughest sell for generic drugs. "When choosing between a branded pioneer biologic and a quasi-generic of uncertain bioequivalence, doctors have been exceptionally reluctant to switch."100

That said, there is some concern that the proposed legislation does not protect the doctor's ability to prescribe the innovative biologic in place of a potential biosimilar. This would make the medical community's acceptance ultimately unimportant. BIO stated that they were concerned that the proposed bill will allow biosimilars to be substituted for the original product without the intervention of the prescribing doctor, thus taking medical decision-making out of the hands of a patient's doctor.101 The FDA agreed, stating, "patients should not be switched form [sic] the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician, and legislation should not allow for determination of interchangeability at this time."102

IV. ANALYSIS

Because the Biologics Act is a compromise between so many interest groups, industry sectors, and individuals, there are still a number of concerns in adopting the legislation. Part A of this Section asks if the compromise reached will be economically efficient, while Parts B and C will draw comparisons to mechanisms for biosimilar approval in other world markets. Parts

99. Id.


102. Id.
D and E then analyze the interplay of the legislation with the patentability requirements of enablement and novelty, respectively.

A. Will The Biologics Act Work Economically?

There are many advantages to using the same regulatory framework in the pending legislation as is used under the Hatch-Waxman Act. The most notable of these is the quarter-century of experience, observation, and troubleshooting that parties have already had with the latter. By using provisions similar to those of the Hatch-Waxman Act, legislators have an idea of how courts will interpret the Act. It also allows use of market data that can give an estimate of effects of the law on various parties. Predictability is invaluable to lawmakers as they attempt to broker the necessary compromises between the disparate interests. Enacting Hatch-Waxman-like provisions also provides the courts with persuasive precedent they can use to interpret the new biosimilars law. Finally, it also provides guidance to the FDA, which will be the entity enforcing the Bill.

The Biologics Act was introduced as the next step in the evolution of the Hatch-Waxman Act, but it is uncertain whether biosimilars are really conducive to a Hatch-Waxman-like process of approval and generic manufacture. The requirements of the Biologics Act, notably the extensive clinical studies required for the application\(^\text{103}\) (unlike an ANDA, which merely requires a showing of bioequivalence—i.e. that the generic compound performs in the same manner as the innovative drug\(^\text{104}\)), will undoubtedly increase biosimilar manufacturer’s costs and decrease the margin between the price of the original and the price of the biosimilar. Initial estimates are that biosimilars will be priced between 10% and 20% lower than the brand-name counterparts.\(^\text{105}\)


\(^{105}\) JEANETTE MARCHANT, THE FUTURE OF BIOSIMILARS (2007) available
compared to an average 71% savings on small-molecule generic drugs. The development costs of biosimilars are also much higher than the $1 million to $2 million expected development costs of a small-molecule generic. The expected cost of development ranges from $10 million to $40 million. When coupled with the possibility that safety concerns might diminish the potential market for biosimilars, this situation might not be economically efficient for any of the parties involved.

In addition to the concerns of higher development costs and lower profit margins, the market for biologics is another concern. Many biologic therapies treat life-threatening diseases. As such, they target a smaller market than most small-molecule compounds. Also, healthcare providers are less likely to utilize price-fixing mechanisms for such therapies. These factors make a sudden and significant drop in price unlikely, even assuming legislation authorizing approval is passed.

It is too early to speculate as to whether an economically efficient equilibrium can be reached between supply and demand for biosimilars in the U.S. market. Thus far, only one biosimilar has been approved by the FDA. As previously mentioned, Omnitrope, a human growth hormone biosimilar, was approved on May 30, 2006, through an ANDA that essentially defined it as a drug rather than a biologic. While this approval process was acceptable for Omnitrope because hGH is comparatively small (it has 191 amino acids and weighs only 22 kilodaltons) and has a relatively simple structure (only 4 helices), it will not be widely

http://www.globalbusinessinsights.com/content/rbhc0187m.pdf (abstract only).


107. MARCHANT, supra note 105.


109. Id. at 1295.

110. See Omnitrope, supra note 70, and accompanying text.

available. Omnitrope is marketed at 75% of the cost of the original compound, and the market reaction to the biosimilar introduction has not yet been studied.

B. A European Model

Since the European Union (EU) passed regulations for biosimilar approval in 2003, we can utilize market data from Europe to predict some of the effects introduction of biosimilars will have on the U.S. market. While the EU system allows for approval of biologics under the regular generic approval process (the equivalent of filing an ANDA with the FDA), it also allows for an alternative route to approval, recognizing the improbability of a true generic biologic. To date, though, only two biosimilar drugs have been approved through the latter route; thus, it is premature to predict the market effects in the U.S. Nonetheless, many believe that the head start biosimilars have acquired in European markets will benefit generic companies with a strong European presence, possibly to the detriment of American-based generic manufacturers.

The European Generic Medicines Association stated that because the EU developed a biosimilar approval system first, it is set to become “the global centre for R&D and production of this new generation of affordable, biotech pharmaceuticals, giving the EU a huge competitive advantage over other countries like the United States and Japan.

Another problem with using European market data to predict the ultimate effects that introduction of biosimilars will have on the U.S. market is that many European countries have price-fixing

112. Roger & Mikhail, supra note 56, at 408.
115. MARCHANT, supra note 105.
mechanisms in place for medication.\textsuperscript{117} If the brand-name drug prices are fixed low enough, it could be difficult for the generic manufacturers to make a profit since expenses for development of biosimilars are much higher than for small-molecule generics.

The European biosimilar approval system differs from the proposed U.S. legislation in several significant ways. First, market exclusivity under the EU system is eight years, with the caveat that a similar drug, though permitted to apply after eight years, cannot actually enter the market for ten years. Second, the type and amount of data required for each application varies on a case-by-case basis. In essence, then, the European Medicines Agency's (EMEA) disclosure requirements of demonstrated safety and efficacy of a biosimilar are essentially product class-specific. A biosimilar application could, therefore, range in specificity from being almost on par with a generic application (merely showing the properties of the proposed generic, with very limited non-clinical/clinical studies), to being nearly as complete and specific as a full, stand-alone application for a novel drug or formulation, depending on which class of products it represents.\textsuperscript{118} However, we will have to wait several more years until we fully understand the impact that these differences will have on the relative success of the systems.

\textit{C. Other International Systems}

In addition to the European market, India has gained a substantial foothold in the market for biosimilars. The Indian Food and Drug Control Administration is responsible for oversight of pharmaceuticals, which include biosimilars. Three conditions must be met before approval is issued for a typical biotech product: (1) the Department of Biotechnology must approve protocols of the animal toxicity studies used; (2) the Drug Controller General of India must approve clinical trials and final product for marketing; and (3) The Food and Drug Control


\textsuperscript{118} \textit{MARCHANT, supra} note 105.
Administration must issue a manufacturing approval. All these approvals can be completed within a year.

In contrast, biosimilar approval only requires clinical trials of 100 patients at an average cost of $100,000. At least seven manufacturers are currently taking advantage of the biosimilar market, though several are still in the planning stages. In May of 2007, Dr. Reddy's, an Indian generic drug manufacturer, released Reditux, a biosimilar version of Rituxan, a monoclonal antibody (MAb) treatment of Non-Hodgkin's Lymphoma. To date, Reditux represents the only biosimilar MAb in the world. However, because Dr. Reddy's used an entirely different process of manufacture than is used for Rituxan, there has been no resulting patent litigation. Reditux is priced 50% lower than Rituxan, which generated global sales of $3 billion in 2006. Dr. Reddy's plans to market Reditux in the United States as soon as mechanisms are in place for FDA approval, which would essentially exclude American generic manufacturers from competing since the foreign competitor would have such a significant head start.

There is less danger to American generic companies from China. China, unlike India, has few generic “powerhouse” companies. Additionally, while Indian companies like Dr Reddy's and Ranbaxy can compete with the American companies as soon as an FDA approval process is established, China has no such companies poised with a similar advantage. For example, one of the largest Chinese biotech companies, 3Sbio, generated only a paltry $12 million marketing erythropoietin in 2006.

Three factors, however, make China ripe for generic expansion. First, with China's lower per capita income, the expense of brand-name biologics is often prohibitive. The three top-selling

119. Dr. Reddy's Laboratories Ltd., founded in 1984, had much of its initial success in countries which did not recognize process patents. This allowed the company to reverse-engineer drugs from the U.S. and Western Europe and sell royalty-free versions of them in Russia and India. By the 1990s, the profits made from these endeavors allowed the company to move into regulated markets such as the U.S. Currently, Dr. Reddy's is the third-largest pharmaceutical company in India with a yearly revenue of $1.5 billion and a presence in over 100 countries across the globe. See generally Dr. Reddy's—About Us, http://www.drreddys.com/coverview/aboutus.htm (last visited Apr. 28, 2008).
biologics—Neupogen, Epogen, and Intron A—cost at least $15,000, $10,000, and $22,000, respectively, per patient per year. Another popular biologic, Cerezyme, costs over $170,000 per patient per year. These prices make the products inaccessible for many who need them. Second, the large population of China compounds the problem of high prices. Third, the close proximity of China to other Asian markets makes it likely that Chinese generic manufacturers will expand in the near future.

It is possible, however, that with numerous recent high-profile quality control scares surrounding imported products from China, American patients and doctors will be unlikely to risk prescribing or taking the imported biosimilar medication. This could make it difficult for Chinese companies to compete effectively in the American market regardless of whether they have a head start.

**D. Having Your Cake and Eating It Too: The Enablement Problem**

The unpredictability of the behavior of biologic compounds during production has consequences not only for production of a true generic, but also for patentability. A biotechnology patentee has the opportunity to deposit biological specimens to aid in the required written disclosure of the invention, as it is sometimes difficult for the written description to adequately illustrate the nature of the invention, but a biotechnology patent is still bound by the same statutory requirements for patentability as any other patent.

Among these patentability requirements is the requirement that the specification of the patent “enable” an individual with skill in

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121. Imported Chinese fish, seafood, toothpaste, toys, tires, and pet food have all been found to have potentially dangerous flaws due to inadequate quality control measures. *See, e.g.*, *Bush Tackles Scares Over Imports*, BBC News, July 18, 2007, http://news.bbc.co.uk/2/hi/americas/6905372.stm.
122. “Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. . . . Biological material need not be deposited, inter alia, if it is known and readily available to the public or can be made or isolated without undue experimentation.” 37 C.F.R. § 1.802(b) (2007).
the relevant art to make and use the invention.\textsuperscript{123} Without enablement, the \textit{quid pro quo} of the U.S. patent system breaks down; the patentee does not provide enough information to the public to merit the embarrassment of a public monopoly.\textsuperscript{124} As summarized in \textit{United States v. Dubilier Condenser Corp.}:

[the inventor] may keep his invention secret and reap its fruits indefinitely. In consideration of its disclosure and the consequent benefit to the community, the patent is granted. . . . [U]pon expiration of the [patent production] period, the knowledge of the invention inures to the people, who are thus enabled without restriction to practice it and profit by its use.\textsuperscript{125}

For example, in \textit{Genentech, Inc. v. Novo Nordisk}, the court struck down a patent directed towards a method for producing a protein of human growth hormone (hGH) amino acids, including the step of cleaving a conjugate protein\textsuperscript{126} through a method called "cleavable fusion expression," even though the method was known and used in similar processes.\textsuperscript{127} The court held that just stating that cleavable fusion expression was possible was insufficient to enable one skilled in the art to practice the method. The court reasoned:

\begin{quote}
Genentech's arguments, focused almost exclusively on the level of skill in the art, ignore the essence of
\end{quote}

\begin{footnotes}
\item[125] \textit{United States v. Dubilier Condenser Corp.}, 289 U.S. 178, 186-187 (1933).
\item[126] A conjugate protein is one attached to the protein or peptide of interest, often done so that the body can recognize the molecule. In order to purify a sample of the protein of interest, however, the conjugate protein must be detached or "cleaved" from it.
\item[127] \textit{Genentech, Inc. v. Novo Nordisk}, 108 F.3d 1361, 1363, 1368 (Fed. Cir. 1997).
\end{footnotes}
the enablement requirement. Patent protection is granted in return for an enabling disclosure of an invention, not for vague imitations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not be carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.  

1. **Impossibility of Replication—the Brand-Name Perspective**

The essence of the arguments over biosimilars in both Congress and the scientific community rests on the fact that the scientific community cannot exactly duplicate biologic compounds, hence the use of the new term “biosimilar” or “follow-on biologic” in place of “biogeneric.” The pharmaceutical companies that lobby against approval of biosimilars have gone to great lengths to demonstrate the impossibility of replicating their work exactly with the current technological limitations. Executives from large pharmaceutical corporations such as Novartis, Johnson & Johnson, and Pfizer have testified before congressional committees and cited public health and safety as a reason to halt the approval of an expedited approval process for biosimilars. They claim that there is no possible way to exactly and safely copy their results. Even with the information provided in their own patent disclosures, including deposited biological samples, the end product is unpredictable. Indeed, the deposited biological samples rarely include samples of their cell lines, but rather just the end product biologic. This gives no aid to anyone attempting

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128. *Id.* at 1366.
129. *See supra* note 60 and accompanying text.
132. *Id.*
133. *See* Hancock Testimony, *supra* note 54 and accompanying text.
to replicate the patent-holder’s process of manufacture—a process which is a prerequisite to achieving the desired biologic. 134

2. Implications for Patentability

If this is indeed the case, then brand-name manufacturers have made a *prima facie* case against their own patent’s enforceability due to nonenablement. Even with samples of the compounds, detailed instructions on the process of manufacture (in some cases), and intimate scientific knowledge of the mechanism of use of the compound and the human body’s reaction to it developed over years of study, the results are still impossible to duplicate, even by one highly skilled in the relevant art. It is in the nature of biologic compounds that the results are unpredictable. And that detection of variation is in some cases impossible until it interacts, often deleteriously, with the patient. 135

However, the fact that it is impossible for the inventor to enable the use of the invention through the written description does not negate the requirement that enablement exist for the subject matter to be patentable. If enablement is itself impossible, then trade secret protection might be more advisable than patent protection, as reverse engineering such a complicated process is highly improbable.

3. Trade Secret Protection as an Alternative

Trade secret law is particularly valuable in situations where the product is valuable, the manufacturer desires protection for longer than the statutory patent term, and there is little likelihood that the product will be copied. 136 However, a patented invention is protected against not only literal infringement, but also under the doctrine of equivalents, 137 which has no counterpart in trade secret law. Here, this would mean that changing one or two unimportant

134. *See supra* notes 59-60 and accompanying text.
135. *See supra* notes 50-51 and accompanying text.
steps in the process of manufacture would still infringe the patented process, while a small change would overcome trade secret protection.

While it might not seem that allowing a patentee to obtain and enforce a patent over a biologic is in line with the notion of equity inherent in the U.S. patent system, where no one else can make use of the patentee’s invention, such patents have been repeatedly upheld without any question as to their validity under 35 U.S.C. § 112.

One of the most recent cases to underscore the strength of the validity of biotechnology patents was Amgen, Inc. v. Hoechst Marion Roussel, Inc. In this case, the patentee sought a declaratory judgment that the defendant infringed five of its patents covering the biologic erythropoietin (EPO). In an extended discussion regarding enablement of the claims, after which the court eventually declared the patents invalid, the nature of biologics and impossibility of enablement were not mentioned. Rather, the court said that the claims were not enabled because the patentee did not disclose how to deposit kidney tumor cells. The court was silent regarding the fact that even if the exact process had been disclosed and duplicated, the outcome would not have been identical. Even while holding that the patent claims in question in this case were not enabled, the court strengthened biotechnology patents as a whole.

There may be a public policy explanation behind the obvious missing pieces in opinions such as Amgen. While the United States is still a world leader in pharmaceutical development, thanks in large part to price-fixing in Europe and Japan, it is lagging in the field of biosimilars. The EU, Japan, China, and India, all have regulations allowing for the approval of biosimilars. An innovative biosimilar segment of the U.S. economy could help ameliorate some of the growing concern over the cost and regulation of healthcare in the U.S. It could reinvigorate the biotechnology sector, and, by extension, the foundering

139. Id. at 1295.
140. Id. at 1307.
141. See supra Section III.
In order to promote continued research and development in biotechnology, however, American patents must be strong enough to protect the ideas they generate. If foreign patents are stronger, or if there are questions about whether biotechnology patents will be interpreted consistently through our patent law, there is little incentive for inventors to file in the U.S. Protecting innovation is crucial for industry growth.

Recently, the U.S. House of Representatives passed H.R. 1908, the Patent Reform Act of 2007. Many of its provisions, such as more accessible reexamination procedures, post-patent review, and third-party prior art submissions are directly aimed at strengthening U.S. patents. According to the Patent Reform Act’s sponsor, Representative Howard Berman stated:

[T]here should be no question that the U.S. patent system produces high quality patents. Since questions have been raised about whether this is the case, the responsibility of Congress is to take a close look at the functioning of the patent system. High patent quality is essential to continued innovation.

This sentiment is shared by many, as the passage of the bill in Congress demonstrates. It is also likely behind the reluctance of the courts and the legislature to address the problem of the lack of enablement in biologic patent specifications. While the goals behind the actions—improving the international reputation of American patents, boosting the biotechnology sector, improving healthcare, decreasing the national debt—are admirable, upholding patents that do not meet the statutory requirements for patentability

142. Healthcare spending comprised 16 percent of the gross domestic product in 2004. More money was spent per capita that same year on healthcare than on food. For a complete discussion, see JULIUS RICHMOND AND RASHI FEIN, THE HEALTH CARE MESS: HOW WE GOT INTO IT, AND WHAT IT WILL TAKE TO GET OUT (2005).
145. Id. at E775.
is confusing and ultimately harmful to U.S. patent law.

E. Patentability Revisited—the Novelty Requirement

Another statutory requirement of patentability is that the claimed invention be "novel." 146 In order to be novel, at least one limitation of the claimed invention must be disclosed or "anticipated" by a prior art reference. Prior art can include a patent, published patent application, journal article, or other reference listed in 35 U.S.C. § 102, assuming that the requisite time constraints are met. The purpose of the novelty requirement is to prevent the issuance of patents covering material in the public domain. If an inventor does not disclose something that was previously unknown to a person of ordinary skill in the relevant art, then he is not entitled to monopoly privileges. As Justice O'Connor has said, "[t]he novelty and nonobviousness requirements of patentability embody a congressional understanding, implicit in the Patent Clause itself, that free exploitation of ideas will be the rule, to which the protection of a federal patent is the exception." 147

In Diamond v. Chakrabarty, 148 the Supreme Court opened the proverbial floodgates to a deluge of biotechnology innovation and litigation when it extended the scope of statutorily patentable inventions to cover the biotech sector. In holding that a genetically engineered bacterium capable of breaking down crude oil was patentable, the Court dispensed with the notion that a living organism could not be patented. 149 The closely-related idea, however, that a naturally-occurring living organism is not patentable, was endorsed by the Court's opinion. 150

146. "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101 (2006) (emphasis added).
149. Id. at 315-16.
explained, a naturally-occurring organism is not novel. Just as discovery of a scientific principle or mathematical formula is not patentable,\(^1\) neither should a hormone or protein complex found \textit{in vivo} be. It may have taken considerable work for Einstein to perfect the famous \(E=mc^2\) equation. It may have taken mental processes that few others in the world could have accomplished, and the result was unmistakably useful. These facts, however, do not make the equation patentable subject matter. It was merely discovered, not truly invented.\(^2\)

The same rationale applies to most biologic therapies. Deducing the steps required to purify and produce insulin, for example, took considerable work by some of the top scientists in the field. Indeed, work began on purification of human insulin for therapeutic purposes as early as 1963, but it was 1982 before Eli Lilly successfully obtained approval to market its insulin therapy.\(^3\) The resulting product is unmistakably useful, even life-saving. These facts, however, and the costs expended in research and development by pharmaceutical companies, do not make insulin patentable subject matter. It is a naturally-occurring molecule, and therefore not "invented."

\textit{F. Taking Intellectual Property—the Constitutional Issue}

The brand-name companies counter these arguments by claiming that it is an unconstitutional taking without just compensation for the FDA to utilize knowledge garnered from their applications and clinical trials to make decisions regarding generic drugs or biologics. Genentech, a large brand-name company, recently filed a citizen petition with the FDA asserting that the agency should not even issue an opinion in the debate over data requirements for biosimilar applications, since they would have the benefit of knowledge garnered from patentees such as Genentech.\(^4\) A "guidance document" issued by the FDA


\(^2\) \textit{Id.}

\(^3\) \textit{MICHAEL BLISS, THE DISCOVERY OF INSULIN} 155 (1982).

\(^4\) \textit{See} Schultz Testimony, \textit{supra} note 67.
represents the agency's current thinking on a given topic. Preparing such a document necessitates using the agency's cumulative knowledge based on all prior approvals and applications, though not the actual data itself.155 The Generic Pharmaceutical Association objected to the petition and is having a thorough constitutional analysis of the issue prepared for distribution to the interested parties.156

Congress needs to address the issues of enablement, novelty, and takings in any bill covering biosimilars. If these issues are not addressed, then the confusion and the friction between the industry, the FDA, and the judicial system will continue to build. While it would take time and litigation to sort out all the contradictions that have emerged even if the bill were passed today, the longer the legislature delays, the more tangled the problem becomes and the more time-consuming the solutions.

V. CONCLUSION

Biologics are the ultimate therapies: unlike traditional drugs, which are substances foreign to the human body that change the way it naturally functions, they are the missing parts of the body itself. For example, instead of taking a drug that affects the cells in the endocrine system and squeezes more hGH out of the pituitary gland, now the hGH itself can simply be supplied. These therapies are the frontier of medicine, and the law must be extended to protect them.

Now that the United States is years behind its foreign counterparts in the biosimilar industry, any proposed legislation attempting to ameliorate the deficiency is welcome, if only to impress upon Congress the urgency of the situation. There is an unmistakable need for an expedited approval process in order to provide incentives for competition in the biologic drug industry. This type of competition, when seen in the small-molecule pharmaceutical sector, was simultaneously responsible for saving consumers billions of dollars and promoting increased spending on research and development for innovative treatments. However, using a Hatch-Waxman approach while requiring almost as many

155. Id.
156. Id.
clinical trials as for an innovative drug is not a workable solution. Large pharmaceutical corporations and consumers may benefit, but there may not be enough profit incentive for the follow-on biologic industry to compete.

The existing patent law should also be considered during the debate over biosimilar legislation. If large pharmaceutical companies are allowed to claim that concern for the public safety and welfare should bar expedited approval processes (and, hence, biosimilars), their patents covering the material should be invalid for lack of enablement. Invalidating these patents would have the dual advantage of advancing public safety concerns by requiring the equivalent of an NDA or BLA from any manufacturer, innovative or follow-on, and of providing an incentive for competition in the biologic sector by removing the hurdle of proving invalidity through costly litigation. However, without any patent protection available for biologics, Congress understandably worries about losing pharmaceutical business in the United States.

Ultimately, the Hatch-Waxman Act can provide a working framework for expedited biosimilar approval. Using it as a mold gives us the advantage of almost a quarter of a century of experience and troubleshooting. Going beyond that, however, and attempting to literally copy and paste the language of the Hatch-Waxman Act into the Biologics Act will not guarantee the same results that the former produced for small-molecule compounds in 1984.

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