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Fixing a Hole: Will Generic Biologics Find a Niche Within the Hatch-Waxman Act?

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Cover Page Footnote

Many thanks to Professors John J. Normile, Partner at Jones Day, and Brian Coggio, Senior Principal at Fish & Richardson P.C., for their guidance.

Fixing a Hole: Will Generic Biologics Find a Niche Within the Hatch-Waxman Act?

Elysa B. Goldberg, Ph.D.*

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INTRODUCTION

The following scene takes place at a common pharmacy counter.

Pharmacist: “There is a generic formulation of this drug. Would you like to buy it instead of the brand-name prescription?”

Consumer: “How much would I save if I bought the generic drug?”

Americans are concerned with the cost of drugs.¹ Currently, America’s health care spending is about \$2 trillion, and in ten years, is expected to roughly double to \$4.1 trillion.² To put that into perspective, we spend about \$7,500 per capita on health care

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¹ See, e.g., Andrew Pollack, *Costly Drugs Known as Biologics Prompt Exclusivity Debate*, N.Y. TIMES, July 22, 2009, at B1, available at <http://www.nytimes.com/2009/07/22/business/22biogenerics.html?pagewanted=all>.

² Orrin G. Hatch, U.S. Sen., Remarks Before the U.S. Chamber of Commerce, *The Future of Biologics—Examining Market Competition, Innovation, and Patient Safety* (Apr. 25, 2007), available at http://www.votesmart.org/speech_detail.php?sc_id=279366&keyword=&phrase=&contain.

in the United States.³ These figures are expected to rise to \$12,800 per capita in 2016.⁴ Much of this increase is expected because of greater spending for pharmaceuticals.⁵ With such a large amount of national spending invested in healthcare, the millions of uninsured or solely Medicaid-covered Americans have a great stake in the price of medication.⁶ Citizens and legislators are concerned because “[p]rices are inexorably linked to healthcare, monetary and fiscal policy, management of national debt, and, ultimately, overall standard of living.”⁷ Thus, the rapid rise in healthcare spending is a deep concern for citizens, drug companies, healthcare providers, and politicians.⁸

To bring a new, innovative drug to market, a pharmaceutical company needs to spend huge sums of money on research and development.⁹ Thousands of chemicals are routinely synthesized in laboratories with the hope that just one chemical will provide a benefit to Americans.¹⁰ Then, labs send the chemical through a barrage of experimentation for characterization.¹¹ Researchers, drug companies, and the United States Food and Drug Administration (“FDA”) need to answer the following questions: what does this chemical do? And, does this drug generate any undesirable effects? After years of testing, very few chemicals are

³ *Id.*

⁴ *Id.*

⁵ *Id.*

⁶ See NLM Gateway, *Out-of-Pocket Price, Prescription Medications and Seniors*, <http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102275591.html> (last visited Aug. 30, 2009).

⁷ A. Taylor Corbitt, *The Pharmaceutical Frontier: Extending Generic Possibilities to Biologic Therapies in the Biologics Price Competition and Innovation Act of 2007*, 18 DEPAUL J. ART TECH. & INTELL. PROP. L. 365, 370 (2008).

⁸ *Id.*

⁹ Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 151 (2003) (“The estimated average out-of-pocket cost per new drug is US\$ 403 million (2000 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 11% yields a total pre-approval cost estimate of US\$ 802 million (2000 dollars).”).

¹⁰ U.S. CONG. BUDGET OFFICE, A CBO STUDY: RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 2 (2006), available at <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>.

¹¹ *Id.*

still contenders for FDA approval.¹² This tumultuous story of innovative drug synthesis and testing occurs everyday, as the industry is constantly looking for the diamond in the rough. As a result, pharmaceutical companies invest more and more money¹³ with the hope that after years of work, innovative drugs will allow them to pay back the deficit caused by research and development.

Few chemicals are able to be considered medicines.¹⁴ When an invention is patented, the inventor must disclose information permitting others to replicate the invention.¹⁵ In return, the inventor receives the right to exclude others from making, using, marketing, and offering for sale or importing the invention.¹⁶ The Hatch-Waxman Act,¹⁷ which amended the Public Health Service Act (“PHSA”),¹⁸ loosened the exclusivity rights of the patentee by permitting other pharmaceutical companies to produce identical chemicals, “follow-on drugs,”¹⁹ faster by permitting them to bypass FDA testing.²⁰ This Act has permitted consumers to choose between brand-name and generic drugs earlier, driving down the cost of drugs by price competition.²¹ However, the drugs in question have mainly been generated *in vitro*, in glass tubes.²²

¹² See DiMasi et al., *supra* note 9, at 159.

¹³ In late 2005, it was estimated that about \$95 billion was spent per year on medical research. Associated Press, *\$95 Billion a Year Spent on Medical Research*, MSNBC, Sept. 20, 2005, <http://www.msnbc.msn.com/id/9407342/>.

¹⁴ Boehringer Ingelheim, Drug Discovery Process, http://www.boehringer-ingenheim.com/corporate/research/drug_discovery_process.asp (last visited Sept. 27, 2009) (stating that only one in over a million screened molecules is investigated in late stage clinical trials and made available to patients).

¹⁵ 35 U.S.C. § 112 (2006).

¹⁶ *Id.* § 154(a)(1).

¹⁷ Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 28, 35 U.S.C.).

¹⁸ Public Health Service Act (PHSA), Pub. L. No. 111-43, 58 Stat. 682 (1944).

¹⁹ Follow-on drugs are drugs that are replicated from a non-innovative pharmaceutical company to compete with the brand-name drug on the market. See Donald Zuhn, *Deloitte White Paper Addresses Unintended Consequences of Follow-on Biologic Regulatory Pathway*, PATENT DOCS, Aug. 27, 2009, <http://www.patentdocs.org/2009/08/deloitte-white-paper-addresses-unintended-consequences-of-followon-biologic-regulatory-pathway.html>.

²⁰ *Id.*

²¹ *Id.*

²² See *infra* note 39 and accompanying text.

Since the Hatch-Waxman Act was enacted, a new hurdle has surfaced: should patentees of biologics, or molecules synthesized *in vivo* (in cells), also have loosened exclusivity rights?

This Note explores why generic biologics should be tested for FDA approval as rigorously as brand-name biologics. This Note argues that the FDA should require the generic companies to provide experimental data showing that their isolated biological molecules have the same concentration, purity, potency, and activity as brand-name biologics.

Part I highlights the legislation that makes drugs available to the public and examines how biological materials do not fit neatly into the current legislation. Part II discusses present responses to the shortcomings of today's legislation. Finally, Part III offers prescriptions to manage this healthcare ailment.

I. THE LONG AND WINDING ROAD OF CURRENT AND PENDING LEGISLATION

The United States is facing a time of change regarding health care reform.²³ There has been a working system in place to permit the approval of innovative small-molecule drugs, but new technology does not fit neatly into this system.²⁴ Accordingly, one must have a comprehensive understanding of current law to best understand how policies play to the opposing interests of the innovative and non-innovative pharmaceutical industries.

A. Testing Innovative Drugs

Branded drugs come to the public through innovation. There are two main parts to the process: research and development, and clinical testing.²⁵ The pre-clinical phase of development starts with basic discovery through research, using both *in vitro* (in glass)

²³ The White House—Health Care Reform, The President's Plan, http://www.whitehouse.gov/issues/health_care/ (last visited Sept. 27, 2009) (detailing President Barack Obama's health care reform plan).

²⁴ BIO, BIO Principles on Follow-On Biologics, <http://www.bio.org/healthcare/followonbkg/Principles.asp> (last visited Oct. 13, 2009).

²⁵ Manthan D. Janodia, Drug Development Process: A Review (Dec. 25, 2007), <http://www.pharmainfo.net/reviews/drug-development-process-review>.

and *in vivo* (in cells) studies.²⁶ Once researchers identify and purify a candidate compound²⁷ after screening against a specific biological target,²⁸ researchers conduct animal studies for further testing.²⁹ The company developing the drug can file an Investigational New Drug (“IND”) application after it obtains positive results from animal studies.³⁰ The FDA then evaluates INDs and grants permission for the drug to be tested on humans.³¹ Thus begins the clinical phases of testing, consisting of three mandatory separate phases.³²

Each of these phases weeds out drugs that are not suitable for general use within the public.³³ Phase I clinical trials test for safety and tolerability of the drug in a small group of human subjects.³⁴ Phase II trials continue testing for safety and tolerability, but also assess the preliminary efficacy of the drug in a much larger pool of volunteers afflicted with the targeted condition.³⁵ Phase III clinical trials involve the largest pool of volunteers and are designed to evaluate the drug in a more diverse population, over a period of several years.³⁶ The drugs that advance through these three phases are submitted as New Drug

²⁶ *Id.*

²⁷ A candidate compound is a chemical that provides a key breakthrough for consequent clinical trials. Franz F. Hefti, *Requirements for a Lead Compound to Become a Clinical Candidate*, BMC NEUROSCIENCE, Dec. 10, 2008, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2604885/>.

²⁸ The Free Dictionary, Biological Target, <http://encyclopedia.thefreedictionary.com/Biological+target> (last visited Sept. 24, 2009) (“A biological target is an enzyme, receptor or other protein that can be modified by an external stimulus. The definition is context-dependent and can refer to the biological target of a pharmacologically active drug compound, or the receptor target of a hormone (like insulin). The implication is that a molecule is “hit” by a signal and its behavior is thereby changed. This term is commonly used in pharmaceutical research to describe the native protein in the body that is modified by a medicinal chemical.”).

²⁹ Hefti, *supra* note 27.

³⁰ Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 565 (2008).

³¹ *Id.*

³² *Id.*

³³ *See id.* at 565–66.

³⁴ *Id.* at 565.

³⁵ *Id.* at 565–66.

³⁶ *Id.* at 566.

Applications (“NDA”s) and new Biologic License Applications (“BLA”s) to the FDA.³⁷

B. The Differences Between Drugs and Biologics

Since 1984, pharmaceutical companies have had an easier opportunity to generate, market, and sell follow-on, or generic, forms of brand name drugs.³⁸ A drug is generally a small molecule that is synthesized *in vitro*.³⁹ Drugs are simple, not requiring any of the chemical modifications that a cell would provide for complex proteins.⁴⁰ A protein, however, is a large organic molecule that is created *in vivo*;⁴¹ hence, it is called a “biologic compound” or “biologic.”⁴² “When two chemically-synthesized drugs are proven bioequivalent, their safety and efficacy can be assumed because two identical drugs will consistently produce the same reactions. However, biologics do not have such characteristics.”⁴³

The structure of a protein is dictated by a series of complex folding patterns, and is generated as the protein is being synthesized.⁴⁴ Additionally, many proteins within the cell also

³⁷ *Id.*

³⁸ See Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360cc; 28 U.S.C. § 2201; 35 U.S.C. §§ 156, 271, 282 (2006)).

³⁹ BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 472 (4th ed. 2002). “In vitro” reactions are carried out in a test tube in the absence of living cells. *Id.*

⁴⁰ Ronald A. Rader, *Biopharmaceutical Terminology: What is a Biopharmaceutical? Part I: (Bio) Technology-Based Definitions*, BIOEXECUTIVE INT’L, Mar. 2005, at 61–62, available at http://www.biopharma.com/BioExec_pt1.pdf.

⁴¹ ALBERTS ET AL., *supra* note 39, at 472. “In vivo” reactions take place inside a living cell. *Id.*

⁴² National Cancer Institute, *Dictionary of Cancer Terms*, http://www.nci.nih.gov/templates/db_alpha.aspx?CdrID=426407 (last visited Oct. 30, 2009). A biological drug is “a substance made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases.” *Id.*

⁴³ Kathleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 MICH. TELECOMM. & TECH. L. REV. 245, 254 (2007).

⁴⁴ See DAVID L. NELSON & MICHAEL M. COX, *LEHNINGER PRINCIPLES OF BIOCHEMISTRY* 159–200 (3d ed. 2000).

require the placement of sugars or fatty acid moieties⁴⁵ on specific regions for proper function.⁴⁶ Because of the complexity of generating proteins, it is impossible to create proteins using the same methodology as researchers use to create and mass-produce drugs.⁴⁷

Each protein has a highly specific and regulated function within the cell;⁴⁸ as such, each protein is required to perform its intended job perfectly.⁴⁹ When a protein malfunctions, the individual cell and the organism suffer.⁵⁰ For example, when the cells within the pancreas fail to produce insulin, the person suffers from Type 1 diabetes mellitus.⁵¹ The only way to reverse the disease is to reintroduce insulin into the person's body.⁵² Insulin is produced within cultured cells, harvested, and purified before being injected into the patient.⁵³ This illustration reveals how the specificity of insulin controls a patient's complete health.⁵⁴

One can easily characterize small molecules by using techniques of mass spectrometry, infrared spectrometry, nuclear magnetic resonance, and x-ray crystallography.⁵⁵ "However, larger biologic molecules can be much more difficult to characterize in detail because they are more variable and

⁴⁵ The Free Dictionary, Moiety, <http://encyclopedia.thefreedictionary.com/moiety> (last visited Oct. 30, 2009). A moiety is a functional group, or part of a molecule, that is responsible for chemical reactions. *See id.*

⁴⁶ NELSON & COX, *supra* note 44, at 1053–54.

⁴⁷ Ed Zimney, *Understanding Biologics: How They Differ From Drugs and Why They Cost More*, EVERYDAY HEALTH, Dec. 2, 2008, <http://www.everydayhealth.com/blog/zimney-health-and-medical-news-you-can-use/understanding-biologics-how-they-differ-from-drugs-and-why-they-cost-more/>.

⁴⁸ REGINALD H. GARRETT & CHARLES M. GRISHAM, *BIOCHEMISTRY* 158 (2d ed. 1999).

⁴⁹ *Id.*

⁵⁰ *See id.* at 159 (“[T]he primary structure facilitates the development of short-range interactions among adjacent parts of the sequence and also long-range interactions among distant parts of the sequence.”).

⁵¹ MedlinePlus, Diabetes Type 1, <http://www.nlm.nih.gov/medlineplus/diabetestype1.html> (last visited Aug. 27, 2009).

⁵² Janet M. Torpy, Cassio Lynn & Richard M. Glass, *Type 1 Diabetes*, 298 *JAMA* 1472, 1472 (1997), available at <http://jama.ama-assn.org/cgi/content/full/298/12/1472>.

⁵³ The Genetic Landscape of Diabetes, History of Diabetes, <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=diabetes&part=A3> (last visited Oct. 31, 2009).

⁵⁴ *Id.*

⁵⁵ Kelleher, *supra* note 43, at 254.

complex”⁵⁶ While analytical tests can determine structure, identity, purity, stability, and activity of such complex molecules, these assays do not determine the safety and efficacy of the product.⁵⁷ Therefore, it is currently impossible to accurately predict the immunogenicity⁵⁸ of a biologic without using clinical testing.⁵⁹

Supplying proteins to repair and save human lives is the new frontier in pharmaceutical companies.⁶⁰ Therefore, it is necessary to determine variability between biologics produced within a generic pharmaceutical company and a brand name pharmaceutical company.⁶¹ A biologic is generally not a bioequivalent; however, it can be biosimilar.⁶²

Whereas generics of chemistry-based medicines are identical copies of the original product, based on a strict definition of “sameness,” a corresponding definition cannot be established for biosimilar medicines because of their nature and the complexity of their manufacturing process. . . . Because the manufacturing process of the products is so complex, extreme care must be taken to ensure that only medicines which have passed stringent safety and efficacy assessment, for example appropriate pre-clinical and clinical tests, are delivered to patients.⁶³

It is necessary for agencies, such as the FDA, to define the terms of biosimilarity to best protect the public.

⁵⁶ *Id.*

⁵⁷ *Id.* at 254–55.

⁵⁸ The Free Dictionary, Immunogenicity, <http://medical-dictionary.thefreedictionary.com/immunogenicity> (last visited Oct. 31, 2009). Immunogenicity is “the property enabling a substance to provoke an immune response, or the degree to which a substance possesses this property.” *Id.*

⁵⁹ Kelleher, *supra* note 43, at 255.

⁶⁰ *See* Biosimilars, Succeeding in the Market of the Future, http://www.pharmafocusasia.com/research_development/biosimilars.htm (last visited Oct. 31, 2009).

⁶¹ *See id.*

⁶² *Id.*

⁶³ EUROPABIO, HEALTHCARE BIOTECH FACT SHEET: BIOLOGICAL AND BIOSIMILAR MEDICINES 3 (2005), available at <http://www.europabio.org/documents/FS-Biosimilar.pdf>.

C. Purifying Enriched Proteins for Use as Biologics

Pharmaceutical companies need to mass-produce recombinant proteins⁶⁴ so that they can ultimately purify these proteins to use as biologics.⁶⁵ Generating a large quantity of protein is difficult because protein is produced within cells.⁶⁶ To gain an appreciation of how challenging this entire process is, it is necessary to understand protein synthesis and purification.

Proteins are large macromolecules that are produced within cells to perform specific functions and are the driving force of innovative biological research.⁶⁷ When generating a large quantity of the desired protein, the targeted protein must be over-expressed⁶⁸ in a regulated environment to maximize the amount harvested.⁶⁹ Researchers introduce recombinant coding DNA (cDNA) into either prokaryotes (cells without nuclei), or eukaryotes (nucleated cells).⁷⁰ *E. coli*,⁷¹ for example, is a bacterium that can generate a large amount of protein in a short period of time, but lacks much of the internal machinery to generate more complex proteins (e.g. proteins modified by a fatty acid or sugar moiety).⁷² Many laboratories will first attempt to over-express proteins in *E. coli* because it is a simple and robust

⁶⁴ Recombinant proteins are encoded by recombinant DNA or generated from a recombinant gene. Free Online Medical Dictionary, Recombinant Protein, <http://medical-dictionary.thefreedictionary.com/recombinant+protein> (last visited Sept. 23, 2009).

⁶⁵ See CARL BRANDEN & JOHN TOOZE, INTRODUCTION TO PROTEIN STRUCTURE 375 (2d ed. 1999).

⁶⁶ *Id.*

⁶⁷ GARRETT & GRISHAM, *supra* note 48, at 107.

⁶⁸ Over-expression is “excessive expression of a gene by producing too much of its effect or product.” Merriam-Webster Online, Overexpression, <http://www.merriam-webster.com/medical/overexpress> (last visited Sept. 23, 2009).

⁶⁹ See BRANDEN & TOOZE, *supra* note 65.

⁷⁰ ALBERTS ET AL., *supra* note 39, at 491–92.

⁷¹ *Escherichia coli* is a “gram negative bacterium widely used in microbiological and genetic research as well as in protein production.” Cytos Biotechnology, Glossary of Biological Terms, <http://www.cytos.com/?id=197> (last visited Oct. 31, 2009).

⁷² See ALBERTS ET AL., *supra* note 39, at 491–92 (explaining how the normal replication mechanisms of a virus with recombinant DNA molecules can produce more than 1,012 identical virus DNA molecules in less than a day, thereby amplifying the amount of the inserted DNA fragment by the same factor).

process.⁷³ However, many complex human proteins generated in *E. coli* will be inactive due to improper protein folding or the absence of protein translational modifications (which *E. coli* does not have the internal machinery to accomplish).⁷⁴ Many proteins must be over-expressed instead in eukaryotic cells to be properly folded and modified.⁷⁵ Thus, while scientists have the ability to introduce cDNA into cells for over-expression, the cells are ultimately in control and regulate the intracellular process.⁷⁶

The ability to purify over-expressed functional protein is at the heart of why generic biologics would be difficult to squeeze into the Hatch-Waxman Act, which provides companies the opportunity to produce generic drugs.⁷⁷ A protein cannot be used as a biologic when it is still preserved within a cell.⁷⁸ The purification process is crucial, as it washes away all other proteins and cellular debris.⁷⁹ If the desired protein was not purified before

⁷³ See Jeffrey G. Thomas & Francois Baneyx, *Protein Misfolding and Inclusion Body Formation in Recombinant Escherichia Coli Cells Overexpressing Heat-Shock Proteins*, 271 J. BIOLOGICAL CHEMISTRY 11141, 11141 (1996) (“It is well established that the high level expression of recombinant proteins in *Escherichia coli* can result in the formation of insoluble aggregates known as inclusion bodies. Since inclusion bodies consist mainly of the protein of interest and are easily isolated by centrifugation, their formation has often been exploited to simplify purification schemes.”).

⁷⁴ See *id.* (“Molecular chaperones are a ubiquitous class of proteins that play an essential role in protein folding by helping other polypeptides reach a proper conformation or cellular location without becoming part of the final structure.”).

⁷⁵ See Max-Planck-Innovation, *Strategies to Enhance Protein Expression in Eukaryotic Cells*, http://www.max-planck-innovation.de/share/technology/0301-3725-MSG-ZE_DE.pdf?PHPSESSID=2b61508e0840eaa5adf0eb9255e5a36 (last visited Oct. 31, 2009).

⁷⁶ See Bryan A. Liang, *Regulating Follow-On Biologics*, 44 HARV. J. ON LEGIS. 363, 372 (2007) (listing the possible changes that may occur during a biologic manufacturing process).

⁷⁷ Kelleher, *supra* note 43, at 249.

⁷⁸ See Theresa Phillips, *About.com, Methods for Protein Purification*, <http://biotech.about.com/od/protocols/a/ProteinPurify.htm> (last visited Oct. 26, 2009) (“The degree of protein purity required depends on the intended use of the protein. For some applications, a crude extract is sufficient. However, for other uses, such as in foods and pharmaceuticals, a high level of purity is required. In order to achieve this, several protein purification methods are typically used, in a series of purification steps.”).

⁷⁹ AMERSHAM PHARMACIA BIOTECH, *PROTEIN PURIFICATION HANDBOOK 7* (1999), available at http://www.biochem.uiowa.edu/donelson/Database%20items/protein_purification_handbook.pdf [hereinafter *PROTEIN PURIFICATION HANDBOOK*] (“The

being injected into an ailing patient, the patient would suffer much more than be cured, as such alien proteins would be attacked by the body.⁸⁰ The patient would act adversely to such an injection and, as a result, would develop an immediate and lasting immune response to all of the unrecognizable proteins introduced into his body.⁸¹ After all, consider that the over-expressed protein was generated from bacterial or eukaryotic (but non-patient) cells. Only protein that will not adversely affect the patient can be introduced into his body.

As protein enrichment and protein purification are crucial to the generation of biological medicine, it is necessary to gain a solid understanding of each process. Both the enrichment process and purification process, which vary significantly for each protein, are and will be treated by the pharmaceutical corporation as trade secrets.⁸² The methodology used to break open the cells, the solutions used to wash the proteins, and how to separate the desired protein from the cellular debris are all examples of how protein purification can be an unpredictable and a highly variable process.⁸³ Because of this purification process and the uncertainty of the purity of the proteins, it would be difficult for companies to replicate brand-name biologics without the necessary trade

development of techniques and methods for protein purification has been an essential prerequisite for many of the advancements made in biotechnology.”).

⁸⁰ See Liang, *supra* note 76, at 375–77 (“[T]here is one central concern for [biologics] that is not present for chemical medicines: the potential for the product to induce an adverse immunologic reaction in a patient whose body sees the drug as a foreign invader, such as a virus or a bacterium. . . . The immunogenicity of biologic drugs appears to be related to a broad array of factors, including the biologic’s structure, the patient’s genetic attributes, the type of biologic in question, impurities in the product, the route of administration, and the frequency of use.”).

⁸¹ *Id.* at 377 (“The human immune response to a biologic product is difficult to predict generally, and this is even more difficult in the face of changes to manufacturing processes.”).

⁸² See Corbitt, *supra* note 7, at 397–99; see also Kelleher, *supra* note 43, at 254.

⁸³ PROTEIN PURIFICATION HANDBOOK, *supra* note 79, at 7 (“Proteins can even be produced in forms which facilitate their subsequent chromatographic purification. However, this has not removed all challenges. Host contaminants are still present and problems related to solubility, structural integrity and biological activity can still exist.”).

secrets.⁸⁴ Thus, even small changes in the process of generating a biologic “could result in a dramatically different final product.”⁸⁵

The most important aspect of this entire process is maintaining the activity of the protein.⁸⁶ If the protein is over-expressed and purified, but is unable to function properly within a patient’s body upon injection, the pharmaceutical company has failed.⁸⁷ Unlike drugs, which are small molecules that eventually break down over time, proteins may just not work at all.⁸⁸ A drop in the activity of proteins can easily occur because of glitches in the purification process.⁸⁹

Researchers must monitor protein purity and activity because such differences can affect the body in a variety of ways.⁹⁰ For example, if a patient’s normal physiological process cannot produce a functional protein, he absolutely requires a perfect biologic. Furthermore, protein activity is crucial for dictating the dosage of the protein.⁹¹ For instance, if a brand-name biologic is twice as active as the generic, twice the amount of the generic biologic would have to be injected into the patient.⁹² Notably, the difference between dosages would suggest that the follow-on biologic is not a bioequivalent, but a biosimilar.⁹³ Whether the

⁸⁴ See *infra* notes 308–10 and accompanying text.

⁸⁵ Gitter, *supra* note 30, at 561.

⁸⁶ Protein Crystallography, Protein Purification in One Day: Introduction, <http://protein-crystallography.org/protein-purification/introduction.php> (last visited Oct. 31, 2009) (stating that almost all proteins lose their activity and crystallization ability during manipulations).

⁸⁷ See *id.* (“[F]or some proteins, even one extra day when they are being kept under conditions normally used for protein purification could be crucial in respect to their activity and crystallization ability.”).

⁸⁸ See Liang, *supra* note 76, at 369 (explaining the composition of a biologic versus a drug).

⁸⁹ See generally PROTEIN PURIFICATION HANDBOOK, *supra* note 79.

⁹⁰ See generally *id.*

⁹¹ See ClinicalTrials.gov, A Phase I, Dose-Escalation Study to Assess the Safety and Biological Activity of Recombinant Human Interleukin-18, <http://clinicaltrials.gov/ct2/show/NCT00500058> (last visited Nov. 10, 2009), as an example of a biologic clinical trial attempting to identify a safe and effective dosage of the interleukin-18 drug, which is a protein in humans.

⁹² See *id.*

⁹³ See Kelleher, *supra* note 43, at 254 (“When two chemically-synthesized drugs are proven bioequivalent, their safety and efficacy can be assumed because two identical drugs will consistently produce the same reactions.”).

research and design teams can generate an equivalent from the beginning (over-expression) to the end (purification process) factors into the importance of trade secrets.⁹⁴

The FDA has previously relied on the Restatement of the Uniform Trade Secrets Act in defining property interests.⁹⁵ Under the Restatement, “[a] trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.”⁹⁶ As a result, trade secrets that pharmaceutical companies keep can and likely will translate into differences between biosimilars.⁹⁷

In summary:

[M]anufacturing 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. Such drugs are thus termed “biosimilar,” since similarity to the biological molecule is all that can realistically be claimed.⁹⁸

⁹⁴ Corbitt, *supra* note 7, at 398.

⁹⁵ Andrew Wasson, *Taking Biologics for Granted? Takings, Trade Secrets, and Off Patent Biological Products*, 2005 DUKE L. & TECH. REV. 4, 5.

⁹⁶ 21 C.F.R. § 20.61(a) (2009); *see also* Wasson, *supra* note 95, at 12 (quoting 21 C.F.R. § 20.61(a)).

⁹⁷ *See* Corbitt, *supra* note 7, at 398.

⁹⁸ *Id.* at 378.

D. *The Hatch-Waxman Act*

1. Overview

Congress passed the Hatch-Waxman Act⁹⁹ in 1984 to balance the competing interests of generic pharmaceutical companies and brand-name pharmaceutical companies.¹⁰⁰ To promote competition with brand-name drug manufacturers, generic pharmaceutical companies need to gain immediate approval for selling the follow-on drug.¹⁰¹ Thus, these companies require a reduced process for drug approval and an accelerated patent litigation process.¹⁰² Meanwhile, brand-name pharmaceutical companies must preserve their profit margins to be able to afford research and development of drugs.¹⁰³

To balance the competing interests of brand-name and generic pharmaceutical companies, the Hatch-Waxman Act permits the filing and evaluation of “Abbreviated New Drug Applications” (“ANDA”s).¹⁰⁴ By securing an ANDA, a company is permitted to generate a generic version of a patented drug.¹⁰⁵ The company must prove that the drug is safe and effective to secure an ANDA;¹⁰⁶ to do this the applicant merely must submit experimental proof that the brand-name drug and the replicated generic are equivalent.¹⁰⁷

An ANDA certifies one of four possibilities: “1) the drug has not been patented; 2) the patent has expired; 3) the generic will not be sold on the market until after the date which the patent will expire; and 4) the patent is not infringed or is invalid.”¹⁰⁸ If the ANDA is filed under the circumstance that the patent is not

⁹⁹ See 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 and 35 U.S.C. § 271(e) (2006)).

¹⁰⁰ *Id.*

¹⁰¹ Corbitt, *supra* note 7, at 372.

¹⁰² *Id.*

¹⁰³ *Id.*

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*

¹⁰⁸ Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 189 (1999).

infringed or is invalid, the applicant must give notice to the patent holder that it has filed an ANDA.¹⁰⁹ The applicant notifies the patent holder under these conditions because filing the ANDA constitutes literal infringement.¹¹⁰ Further, the ANDA is processed, but final approval is not granted during the thirty month stay in order for both parties to litigate the allegation of invalidity and/or non-infringement.¹¹¹

The patent-holder has forty-five days to file suit for infringement in order to obtain the benefit of the thirty month stay of approval.¹¹² If the patent-holder chooses to file suit, the FDA will not grant final approval of the ANDA for thirty months, permitting litigation between the parties.¹¹³ The brand-name pharmaceutical company could win patent term extensions and market exclusivity provisions,¹¹⁴ while the generic company could win 180 days of market exclusivity for the generic equivalent of the drug.¹¹⁵ Thus, while ANDAs give the generic companies the ability to quickly begin marketing and selling a bioequivalent product,¹¹⁶ the brand-name companies enjoy the notice requirement with the possibilities of term extensions and market exclusivity.¹¹⁷

2. Hatch-Waxman Act Application to Generic Biologics

Congress has tried to apply the Hatch-Waxman Act to biologics.¹¹⁸ Biologics are complex proteins that are manufactured within cells (*in vivo*), not in test tubes (*in vitro*).¹¹⁹ Currently, however, some of the smaller biological matter is classified as

¹⁰⁹ *Id.* at 190.

¹¹⁰ Corbitt, *supra* note 7, at 373.

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.*

¹¹⁴ *Id.*

¹¹⁵ *Id.*

¹¹⁶ *Id.*

¹¹⁷ *Id.*

¹¹⁸ See H.R. 5629, 110th Cong. (2008); S. 1695, 110th Cong. (2007); H.R. 1956, 110th Cong. (2007); H.R. 1038, 110th Cong. (2007).

¹¹⁹ Liang, *supra* note 76, at 369 (describing how biologics production introduces DNA into a cell line); see also ALBERTS ET AL., *supra* note 39, at 472 (explaining *in vivo* and *in vitro* procedures).

“drugs” to permit Hatch-Waxman application.¹²⁰ Two sections of the Hatch-Waxman Act are utilized for small-molecule drugs: section 505(j) and section 505(b)(2) of the Food, Drug, and Cosmetic Act (“FDCA”).¹²¹

The more prevalently used section of the Hatch-Waxman Act for small-molecule drugs is section 505(j) of the FDCA, which permits an applicant to file an ANDA.¹²² This section established the ANDA approval process, allowing cheaper generic forms of approved innovator drugs to be approved and brought on the market.¹²³

An ANDA applicant must include in the ANDA a patent certification described in section 505(j)(2)(a)(vii) of the Act. The certification must make one of the following statements: (I) no patent information on the drug product that is the subject of the ANDA has been submitted to [the] FDA; (II) that such patent has expired; (III) the date on which such patent expires; or (IV) that such patent is invalid or will not be infringed by the manufacture, use or sale of the drug product for which the ANDA is submitted. This last certification is known as a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA refers. The submission of an ANDA for a drug product that is claimed in a patent is an infringing act if the drug product that is the subject of the ANDA is intended to be marketed before the expiration of the patent and, therefore,

¹²⁰ Liang, *supra* note 76, at 390.

¹²¹ Federal Food, Drug, and Cosmetic Act § 505(b)(2), 21 U.S.C. § 355(j) (2006).

¹²² Kelleher, *supra* note 43, at 249.

¹²³ See U.S. DEP'T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, GUIDANCE FOR INDUSTRY, 180-DAY GENERIC DRUG EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (1998), available at <http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/ucm079342.pdf>.

may be the basis for patent infringement litigation.¹²⁴

Section 505(j)(5)(B)(iv) further provides an incentive for generic manufacturers to file paragraph IV certifications. This section states that, in certain circumstances,

an ANDA applicant whose ANDA contains a paragraph IV certification is protected from competition from subsequent generic versions of the same drug product for 180 days after either the first marketing of the first applicant's drug or a decision of a court holding the patent that is the subject of the paragraph IV certification to be invalid or not infringed.¹²⁵

Section 505(j) reflects Congress' intentions to balance encouraging innovation with the need to provide cheaper alternatives to the American public.¹²⁶

The less utilized section of the Hatch-Waxman Act is section 505(b)(2). The FDA has only been able to approve biological therapies using section 505(b)(2) when these compounds are classified as drugs, despite being biologics.¹²⁷

Created in 1984 as part of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, the 505(b)(2) application is intended to encourage sponsors to develop innovative medicines using currently available products. According to Section 505(b)(2) guidelines, an NDA approval can be obtained for a new drug without conducting the full complement of safety and

¹²⁴ *Id.* at 3–4.

¹²⁵ *Id.* at 4.

¹²⁶ *Follow-on Protein Products: Hearing on Safe and Affordable Biotech Drugs Before H. Comm. on Oversight and Government Reform*, 110th Cong. (2007), available at <http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm> (statement of Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer, Food and Drug Administration).

¹²⁷ Nathan A. Beaver & Kelly A. Hoffman, *Final Word: Omnitrope's Approval: What Does it Mean for Other Generics?*, BIOPHARM INT'L, Aug. 1, 2006, <http://biopharminternational.findpharma.com/biopharm/article/articleDetail.jsp?id=361018>.

efficacy trials and without a “right of reference” from the original applicant. . . . [505(b)(2)] proposes a limited change to a previously approved product, but demonstrates the required safety and efficacy of the change.¹²⁸

Some examples of generic drugs that the FDA has approved using this section are recombinant follitropin beta (Follistim®), recombinant human glucagon (GlucaGen®), and human growth hormone (Omnitrope®).¹²⁹ Section 505(b)(2) is essentially a hybrid between a NDA and an ANDA, as applicants may rely on the experimentation conducted by a third party, including the innovative manufacturer, to show the safety of their own products.¹³⁰ The applicant need not perform many of the trials himself if he proves the “relevance and applicability” of any previous clinical findings.¹³¹ Thus, the applicant can evade much of the cost associated with seeking FDA approval of a new drug.

The FDA is hesitant to approve more complex biological therapies under section 505(b)(2).¹³² While the FDA has approved biologic drugs under section 505(b)(2), such as menotropins, glucagon, and calcitonin, generally the FDA maintains that follow-on biologics “present unique and difficult questions that will be addressed in a timely manner.”¹³³ Therefore, the use of this pathway within the Hatch-Waxman Act is limited. Use of this provision would require biological substances to gain approval as new drugs under the FDCA or the Hatch-Waxman provision, as approved under the PHSA.¹³⁴ However, this is unlikely, as Congress is not considering any legislation that would clarify or expand FDA authority to regulate and approve generic

¹²⁸ Kenneth V. Phelps, *The 505(b)(2) Alternative—An NDA That Saves Time and Money*, DIA FORUM, Mar. 2005, available at <http://www.camargopharma.com/Userfiles/Docs/camargo-505b2.pdf>.

¹²⁹ See Liang, *supra* note 76, at 393–97.

¹³⁰ Kelleher, *supra* note 43, at 250.

¹³¹ *Id.*

¹³² *Id.* at 251.

¹³³ Kenneth D. Growth, *Biosimilars Shake Up the Biologics Market*, GENETIC ENGINEERING NEWS, Dec. 1, 2005, at 48, available at <http://www.genengnews.com/articles/chitem.aspx?aid=1159&chid=0>; see also Beaver & Hoffman, *supra* note 127.

¹³⁴ Beaver & Hoffman, *supra* note 127.

biologics.”¹³⁵ Thus, section 505(b)(2) is not a practical pathway to pursue to gain generic approval of biological material as the FDA has expressed discomfort in using this pathway for this exact reason.¹³⁶

3. The Uncertain Future of the Hatch-Waxman Act

Since there has not been a uniform approval process for producing generic biologics under existing United States law, Congress attempted to enact the Biologics Act of 2007.¹³⁷ At the Biosimilars Conference in 2007, Representative Henry Waxman stated that biotechnology drugs embody the future of medicine, as there were almost 500 new such drugs in development.¹³⁸ The FDA has not regulated the majority of new biologics as new drugs under the FDCA, but instead under the PHSA.¹³⁹ Thus, an applicant would file a biologics application (“BLA”), but not a NDA.¹⁴⁰ A BLA confirms the safety and purity of the drug.¹⁴¹ Companies, however, may not file a BLA for most biosimilars due to current practice.¹⁴² The FDA has only approved the smaller, simpler biological “drugs” for manufacture through an NDA, such as insulin and human growth hormone (“HGH”).¹⁴³ Therefore, companies may manufacture the drugs generically through an ANDA.¹⁴⁴ It is not clear, however, why few biologically based drugs are permitted through this process.¹⁴⁵ There are also currently no guidelines to lead manufacturers in filing a NDA or a BLA application.¹⁴⁶

There is still no clear process for approval for generic biologics. An illustration of how the absence of such guidelines

¹³⁵ *Id.*

¹³⁶ *Id.*

¹³⁷ See Congressman Henry A. Waxman, Remarks at Biosimilars 2007 Conference (Sept. 24, 2007), available at <http://www.biosimilarstoday.com/Waxman.pdf>.

¹³⁸ *Id.*

¹³⁹ Kelleher, *supra* note 43, at 251.

¹⁴⁰ Liang, *supra* note 76, at 392.

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ See *id.* at 390–97.

¹⁴⁴ See *id.*

¹⁴⁵ *Id.*

¹⁴⁶ Liang, *supra* note 76, at 392.

affects competition is the court decision in *Sandoz, Inc. v. Leavitt*.¹⁴⁷ Sandoz, Inc. (“Sandoz”) was a generic drug subsidiary of Novartis, one of the largest multi-national pharmaceutical companies.¹⁴⁸ Sandoz sued Michael Leavitt, the Secretary of Health and Human Services, and Andrew Von Eschenback, the acting Commissioner of the FDA, because Sandoz wanted to sell Omnitrope.¹⁴⁹ Omnitrope was going to be a follow-on drug comparable to Genotropin, a substitute for HGH.¹⁵⁰ Low levels of HGH cause various growth disorders and Genotropin could alleviate this condition.¹⁵¹ To market and sell Omnitrope, Sandoz submitted an ANDA to the FDA in 2003 and stated that this follow-on drug was safe and identical to the pioneer drug, Genotropin.¹⁵² The FDA deferred its decision and did not act within 180 days; therefore, Sandoz filed suit.¹⁵³ At the time, like today, there was still no clear process for approval:

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.¹⁵⁴

The *Sandoz* court sidestepped the issue of defining a process for approving the production of generic biologics.¹⁵⁵ It directed

¹⁴⁷ 427 F. Supp. 2d 29 (D.D.C. 2006).

¹⁴⁸ *Id.* at 31–32.

¹⁴⁹ *Id.* at 32.

¹⁵⁰ *Id.*

¹⁵¹ *Id.* at 31.

¹⁵² *Id.* at 32.

¹⁵³ *Id.*

¹⁵⁴ *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary, 108th Cong. (2004)* (statement of William Schultz, Partner at Zuckerman Spaeder, LLP), available at http://judiciary.senate.gov/hearings/testimony.cfm?id=1239&wit_id=3627.

¹⁵⁵ See *Sandoz*, 427 F. Supp. 2d at 41.

the FDA to immediately decide whether to approve the license of Omnitrope.¹⁵⁶ The FDA then approved Omnitrope as a “follow-on protein product” but not as a biologic.¹⁵⁷ The FDA further expressed that the approval of Omnitrope did not carve out a guaranteed pathway to gain approval of other biosimilars.¹⁵⁸ Some have suggested that Congress should take legislative action in response to the district court decision in *Sandoz*.¹⁵⁹

In addition, it may be necessary to create legislation to clarify the FDA’s role and responsibilities in the approval process.¹⁶⁰ There has been an increased need to have a process promptly put in place because the first generation of biologic therapies will expire in 2015.¹⁶¹ The public need for competition will not be met if there is no expedited pathway for approval of generic biologics.¹⁶² Importantly, applicants attempting to gain approval for the manufacture of generic biologics must also submit: 1) analytical studies demonstrating biosimilarity, 2) animal studies, and 3) a minimum of one clinical study that demonstrates safety, purity, and potency.¹⁶³ Since analytical studies, animal studies, and clinical studies take years to perform, competition between innovative and follow-on biologics could be compromised.

Additionally, Representative Waxman has concerns regarding the length of brand-name exclusivity. Representative Waxman argues that a reasonable term of exclusivity is “not one that is so long that it would rob the American people of the cost-saving appropriate generic competition brings,”¹⁶⁴ and that such a term should be less than ten years.¹⁶⁵ While it is important that generic biologics must become available to drive costs down and facilitate competition, incentives for brand-name pharmaceuticals must

¹⁵⁶ *Id.*

¹⁵⁷ Kelleher, *supra* note 43, at 251.

¹⁵⁸ *Id.* at 251–52.

¹⁵⁹ *Id.* at 252.

¹⁶⁰ Corbitt, *supra* note 7, at 381.

¹⁶¹ *Id.*

¹⁶² *See* Kelleher, *supra* note 43, at 252.

¹⁶³ *See* Liang, *supra* note 76, at 384–85.

¹⁶⁴ *See* Waxman, *supra* note 137.

¹⁶⁵ *See id.*

remain high.¹⁶⁶ Those against the Waxman Bill believe that if it becomes easier for generic biologics to compete with brand-name biologics and/or the term of exclusivity is significantly abbreviated, innovative pharmaceutical companies will lose incentive to continue current research and development.¹⁶⁷

Despite Representative Waxman's optimism for the future of generic biologics, many economists challenge the idea that access to follow-on biologics will decrease prices for consumers.¹⁶⁸ Economists estimate that the cost of producing and experimenting upon generic biologics will be a great deal higher than with small-molecule drugs.¹⁶⁹ "The cost associated with getting a biogeneric to market could be tens of millions of dollars, as compared to a couple of million dollars for traditional generics."¹⁷⁰ Additionally, biologics have more specific, targeted activities compared to small molecule drugs.¹⁷¹ This translates to smaller markets that are interested in investing in such therapies.¹⁷² Thus, one can easily argue that very few companies are likely to prosper in generating follow-on biologics.¹⁷³

E. What Americans Can Learn from the EU

On the other hand, the European Union ("EU") has a system that permits generic biologic approval and has saved several billion dollars from the market entry of only a few products.¹⁷⁴ The EU established a regulatory approval process for biosimilar medicines

¹⁶⁶ Donald Zuhn, *BIO CEO Makes Case for 12-Year Data Exclusivity Period*, PATENT DOCS, Aug. 16, 2009, <http://www.patentdocs.org/2009/08/bio-ceo-makes-case-for-12year-data-exclusivity-period.html>.

¹⁶⁷ *See id.*

¹⁶⁸ *See* Suzanne M. Sensabaugh, *Biological Generics: A Business Case*, 4 J. GENERIC MED. 186, 188–89 (2007).

¹⁶⁹ *See id.* at 189.

¹⁷⁰ Kelleher, *supra* note 43, at 253.

¹⁷¹ *See* Liang, *supra* note 76, at 369.

¹⁷² *See generally* U.S. CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 13–35 (1998), available at <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf>.

¹⁷³ *See generally id.*

¹⁷⁴ Kathleen Jaeger, GPhA President and CEO, GPhA Speech at Windhover FDA/CMS Summit (Dec. 5, 2006), available at <http://www.gphaonline.org/resources/2006/12/04/gpha-speech-windhover-fdacms-summit>.

in Europe in 2006, when the European Commission approved the first biosimilar medicines.¹⁷⁵

All biotechnology medicines, including biosimilar biotechnology-derived medicines, are or will be assessed by the European Medicines Agency in London (EMA), which constitutes the scientific body of the European Commission responsible for the evaluation of medicines. They are approved by the European Commission based on the positive scientific opinion issued by the EMA.

When the EMA assesses data for a biosimilar medicine, the scientific principles for ensuring product quality, safety and efficacy are identical to those applied to the originator/brand reference medicine with which comparability is demonstrated.

In addition to the quality data required for all biotechnology products, the companies involved in the developing biosimilar medicines must additionally submit “comparability data.” Indeed, manufacturers must characterize, in parallel, both their biosimilar product and the originator reference product. They must demonstrate, with a high degree of certainty, that the quality of the biosimilar medicine is comparable to the originator/reference medicinal product. A comparability programme is clearly defined and agreed upon in advance with the EMA, who defines the set of non-clinical and clinical data that are necessary to sufficiently demonstrate biosimilarity. The extent of this data varies according to the type and complexity of the medicine involved. Each individual biosimilar medicine is assessed on a case-by-case basis.¹⁷⁶

In addition, the EU states that patients can be assured of safety because of two systems: regulations require that the European

¹⁷⁵ Liang, *supra* note 76, at 399–400.

¹⁷⁶ European Generic Medicines Association, FAQ on Biosimilar Medicines, http://www.egenerics.com/doc/FAQ_biosimilars.pdf (last visited Aug. 27, 2009).

pharmaceutical companies monitor the use and effects of their medicines and provide that a Risk Management Plan is required for each new biosimilar medicine.¹⁷⁷

The EU notes that “[t]he price differential between a reference product and a biosimilar medicine will depend on the relative development costs.”¹⁷⁸ While the EU is optimistic about the relative savings courtesy of biosimilars, development costs may compromise savings.¹⁷⁹

F. *The Public Health Service Act*

1. *Biologics in the Eyes of the Public Health Service Act*

A biological product, as defined by the PHSA, is “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”¹⁸⁰ Some examples of biologics include some vaccines, and monoclonal antibodies, which can aid in the treatment of cancer, anemia, hepatitis, and multiple sclerosis.¹⁸¹

Biologic product sales are continually increasing, with American product sales jumping from \$32.8 billion to \$56 billion from 2005 to 2006.¹⁸² Global sales are expected to reach \$105 billion by 2010.¹⁸³ In the past ten years, the patents of more than a dozen high-profit biologics have expired, creating \$11.5 billion in combined annual sales of off-patent biologics.¹⁸⁴

¹⁷⁷ *Id.*

¹⁷⁸ *Id.*

¹⁷⁹ *See id.*

¹⁸⁰ 42 U.S.C. § 262(i) (2006).

¹⁸¹ Kelleher, *supra* note 43, at 247.

¹⁸² Gregory Roumeliotis, *FDA Under Pressure to ‘Open the Floodgates’ for Biogenerics*, IN-PHARMA TECHNOLOGIST.COM, Aug. 17, 2006, <http://www.in-pharmatechnologist.com/news/ng.asp?n=69925-fda-biogenerics-insulin-hgh-omnitrope>.

¹⁸³ Kelleher, *supra* note 43, at 247.

¹⁸⁴ Meredith Wadman, *Copycats Gear Up to Dog Biotech Brands*, NATURE, Oct. 5, 2006, <http://www.nature.com/nature/journal/v443/n7111/full/443496a.html>.

With a few exceptions, generic biologics have not been able to enter the market due to the current regulatory scheme.¹⁸⁵ One method of approving generic biologics is by enlarging the Hatch-Waxman Act.¹⁸⁶ However, because biological products are highly complex and vary vastly from generic drugs, a new regulatory scheme would need to be put in place for generic biologics to compete.¹⁸⁷

2. Comparison to the Food, Drug, and Cosmetic Act

The regulation of biological products is unique from small-molecule drugs. Most biologics are not regulated as drugs under the FDCA but are instead licensed under section 351 of the PHSa and then evaluated by the Center of Biologics Evaluation and Research (“CBER”).¹⁸⁸ Under the PHSa, each biologic must secure a license, which validates the product as safe and pure.¹⁸⁹ The PHSa does not contain a provision for follow-on biologic approval.¹⁹⁰

Whereas the PHSa ostensibly applies to most or all biologics, the FDCA, on the other hand, has decided to regulate a small number of biologics, such as insulin and HGH.¹⁹¹ Despite providing no clear explanation as to why only these biologics are regulated by the FDCA, such regulation falls under the FDCA.¹⁹² The FDCA’s definition of a “drug” includes “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.”¹⁹³ Thus, this language suggests that the FDCA’s regulation encompasses biological materials as well as drugs.¹⁹⁴

¹⁸⁵ Liang, *supra* note 76, at 409.

¹⁸⁶ *Supra* note 2.

¹⁸⁷ Wasson, *supra* note 95, at 3.

¹⁸⁸ *Id.* at 4.

¹⁸⁹ *Id.*

¹⁹⁰ *Id.*

¹⁹¹ Kelleher, *supra* note 43, at 249.

¹⁹² Wasson, *supra* note 95, at 9.

¹⁹³ 21 U.S.C. § 321(g)(1)(B) (2006).

¹⁹⁴ *Id.*

G. A Tale of Two Bills: The Next Chapter

President Obama's 2010 budget proposal creates an abbreviated pathway for follow-on biologics.¹⁹⁵ The 111th Congress will consider two competing pieces of legislation: House Bill 1427 (the Waxman Bill)¹⁹⁶ and House Bill 1548 (the Eshoo Bill).¹⁹⁷ The Waxman Bill and the Eshoo Bill would amend the PHSa to add a subsection permitting follow-on biologics to enter the market.¹⁹⁸ The two issues that are at the heart of these bills are: 1) the term of exclusivity of the pioneer company, and 2) the evidence required to show that the generic biologic is biosimilar to the pioneer biologic.¹⁹⁹ Congress considered similar legislation in past years, but the current presidential and bipartisan support will likely lead to enactment of a generic approval.²⁰⁰ While the Waxman Bill favors quicker public access to generic biologics,²⁰¹ the Eshoo Bill encourages more testing before approving the biologic.²⁰²

Generic manufacturers support the Waxman Bill, while innovative manufacturers favor the Eshoo Bill.²⁰³ Both the Waxman Bill and the Eshoo Bill will permit the FDA to license biologics deemed "biosimilar."²⁰⁴ The Waxman Bill defines "biosimilar" by stating that "no clinically meaningful differences between the biological product [follow-on biologic] and the reference product [innovative biologic] would be expected in terms of the safety, purity, and potency if treatment were to be initiated

¹⁹⁵ See Barbara Carter, *Congress Answers the Call to Permit Generic Versions of Biologic Drugs*, SUNSTEIN INTELL. PROP. UPDATE, Mar. 2009, <http://www.bromsun.com/publications-news/news-letters/2009/03/200903biologics.html>.

¹⁹⁶ H.R. 1427, 111th Cong. (2009).

¹⁹⁷ H.R. 1548, 111th Cong. (2009).

¹⁹⁸ Rep. Eshoo Proposes Draft Biogenerics Bill, FDA Law Blog, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2008/02/a-peek-inside-p.html (Feb. 18, 2008, 07:26 EST).

¹⁹⁹ H.R. 1548, 111th Cong. (2009); see also FDA Law Blog, *supra* note 198.

²⁰⁰ Ramon Tabtiang et al., *Congress Considers Competing Biosimilar Legislation*, FISH NEWS, <http://fr.com/news/articledetail.cfm?articeid=939>.

²⁰¹ Carter, *supra* note 195.

²⁰² *Id.*

²⁰³ Tabtiang et al., *supra* note 200.

²⁰⁴ *Id.*

with the biological product instead of the reference product.”²⁰⁵ Both bills require generic biologic applicants to submit data indicating that any biogeneric has highly similar molecular structure to the reference product.²⁰⁶

A key assertion in the Eshoo Bill is that a generic biologic is not identical to the innovative biologic.²⁰⁷ The Eshoo Bill states that a generic biologic can never be substituted for an innovative, pioneer biologic.²⁰⁸ Additionally, the Eshoo Bill requires analytical and animal studies to show that the follow-on biologic is highly similar to the innovative biologic.²⁰⁹ This bill will permit the FDA to waive these tests, but only after requesting and considering public comments regarding the balancing of price competition and safety.²¹⁰

The Waxman Bill, on the other hand, proposes comparatively lenient standards for determining equivalence between pioneer and follow-on biologics.²¹¹ This bill proposes that a follow-on biologic only have “highly similar molecular structural features” or have “interchangeability with” the pioneer drug.²¹² Generic drug companies can easily satisfy this requirement, as these companies may use the clinical studies and efficacy tests initially performed by the pioneer company.²¹³ Thus, this bill does not require the pharmaceutical company to perform further testing.²¹⁴

The Eshoo Bill and the Waxman Bill also differ with respect to exclusivity. The Eshoo Bill allows for twelve years of data exclusivity and provides up to two more years for a new use approved for the pioneer biologics.²¹⁵ However, the Waxman Bill suggests a short exclusivity period of five and a half years, and

²⁰⁵ H.R. 1427, 111th Cong. § 3(k)(1) (2009).

²⁰⁶ Tabtiang et al., *supra* note 200.

²⁰⁷ H.R. 1548, 111th Cong. (2009).

²⁰⁸ *Id.*

²⁰⁹ *Id.*

²¹⁰ *Id.*

²¹¹ Carter, *supra* note 195.

²¹² *Id.*

²¹³ *Id.*

²¹⁴ *Id.*

²¹⁵ H.R. 1548, 111th Cong. (2009).

three more years of data exclusivity for new uses and formulations of the innovative biologic.²¹⁶

II. CARRY THAT WEIGHT: HOW PENDING LEGISLATION ALTERS THE CURRENT MODEL

There are great concerns about how amendments to the Hatch-Waxman Act, in the form of the Waxman and Eshoo Bills, may change the face of patent law. A patent requires the inventor to release information that would allow a person having ordinary skill in the art to recreate the invention completely.²¹⁷ However, it is inherent in the definition of a “biologic” that such molecules are much more difficult to recreate than small molecule drugs.²¹⁸ Biologics, which researchers and companies grow and harvest *in vivo*, present many hurdles that make them difficult to recreate in the form of generics.²¹⁹ Because it is so difficult to recreate biologics, the patent requirement of enablement²²⁰ is trickier to satisfy and makes it more difficult to generate generic biologics.²²¹ Despite this strain on the patent system, there is an enormous and still growing need for generic biologics.²²² The mounting necessity for generic biologics puts a strain on two opposing needs: 1) the need for generic biologics to slash costs,²²³ and 2) the requirement that all biologic medication being sold is bioequivalent to the innovative biologic and is safe to use.²²⁴

²¹⁶ H.R. 1427, 111th Cong. (2009).

²¹⁷ Corbitt, *supra* note 7, at 397.

²¹⁸ *See id.* at 377.

²¹⁹ *Id.* at 378.

²²⁰ 35 U.S.C. § 112 (2006) (stating that the specification must describe how to make and use the invention to one skilled in the art); *see also* United States Patent and Trademark Office, 2164 The Enablement Requirement [R-2]—2100 Patentability, http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2164.htm (last visited Oct. 16, 2009).

²²¹ *See* Corbitt, *supra* note 7, at 367–68.

²²² *Id.* at 369.

²²³ *Id.*

²²⁴ *Id.* at 372.

A. The Intersection Between Patent Law and Biologics

Because of the chemical differences between simple small-molecule drugs and complex biological compounds, several problems arise when trying to apply the current Hatch-Waxman provisions to biological compounds.²²⁵ Biologic compounds are larger and more complex than small-molecule drugs, requiring a more sophisticated and regulated methodology of production.²²⁶ Because of the intricacies in producing sensitive biologics, small changes in production could have severe and far-reaching consequences in a patient's health.²²⁷

Besides the health concerns associated with taking generic forms of biologic compounds, there are general concerns about the impact of biologic legislation on United States patent law.²²⁸ "First, if it is impossible to synthesize an identical compound the effect could be to preclude patentability on the grounds of 'enablement.'"²²⁹ The patent-holders, the brand-name pharmaceutical companies, would walk a thin line if required to argue the conflicting ideas that their product is enabled and yet it is impossible to replicate due to the nature of production.²³⁰ Second, patentability is questioned because many biologics are compounds already produced, *in vivo*, in every healthy human being.²³¹ Thus, while the process of generating large quantities of any biologic can be novel, the biological compound may not meet the patentability requirement of novelty.²³² The legislators must consider these problems before they assume that the parameters set in place by the Hatch-Waxman Act, written for competition of small-molecule drugs,²³³ will directly apply to biologics.

In addition to enablement for patent eligibility, one must also show novelty. To be novel, an invention must be new, unknown to

²²⁵ *Id.* at 397.

²²⁶ *See supra* notes 41–59.

²²⁷ Corbitt, *supra* note 7, at 366–67.

²²⁸ *Id.* at 367.

²²⁹ *Id.*

²³⁰ *Id.* at 367–68.

²³¹ *Id.* at 368.

²³² *Id.*

²³³ *Id.*

the public, and not published (or described in a pending U.S. patent application) anywhere.²³⁴ *Diamond v. Chakrabarty*, a landmark Supreme Court case, allowed biotechnology innovation to fall within the scope of statutorily patentable inventions.²³⁵ The Court stated that a living organism can be patentable as long as it was not naturally-occurring.²³⁶ Thus, discoverable matter is not patentable, while inventions are patentable.²³⁷ This principle extends to the biological therapies that would be encompassed by the Biologics Act, if the legislation passes. For example, a purified protein is patentable because there is a difference between pure and impure materials.²³⁸ Thus, a patentable innovation can be the actual purification process, despite the fact that the product itself is naturally-occurring.

B. Why Push for Generic Biologics?

As discussed earlier,²³⁹ Americans are deeply concerned about the cost of drugs,²⁴⁰ and they have therefore embraced generic alternatives. Generic alternatives have also made a lasting impression on the pharmaceutical industry.²⁴¹ Ten years after the Hatch-Waxman Act was passed in 1994, Americans saved between \$8 and \$10 billion in drug stores by purchasing generic drugs instead of brand-name drugs.²⁴² Americans have shown the pharmaceutical companies that they want to decide between a brand-name form of a small-molecule drug and the generic equivalent, and that they want to save money.²⁴³ This financial need for cheaper drugs translates into the public wanting and needing competition between brand-name and generic biologics.²⁴⁴

²³⁴ 35 U.S.C. § 102 (2006).

²³⁵ *Diamond v. Chakrabarty*, 447 U.S. 303, 316 (1980) (“A rule that unanticipated inventions are without protection would conflict with the core concept of the patent law that anticipation undermines patentability.”).

²³⁶ *See id.* at 317.

²³⁷ *Id.* at 309.

²³⁸ *In re Bergstrom*, 427 F.2d 1394, 1402 (C.C.P.A. 1970).

²³⁹ *See supra* notes 1–8 and accompanying text.

²⁴⁰ *See supra* note 1 and accompanying text.

²⁴¹ *See* U.S. CONG. BUDGET OFFICE, *supra* note 172.

²⁴² *Id.* at ix.

²⁴³ *See id.*

²⁴⁴ *Id.* at x.

By facilitating price competition through passing new legislation, for example via the Eshoo Bill or Waxman Bill, more follow-on biologics would be available to patients.²⁴⁵

Generic drugs, though, have hampered the innovative pharmaceutical industry's ability to recover investment costs.²⁴⁶ Investment in research and development has increased from 14.7% to 19.4%, while sales rose from \$17 billion to \$57 billion between 1983 and 1995.²⁴⁷ These ascending numbers, however, hardly account for innovative pharmaceutical companies branching out in research and development more rapidly, resulting from generic pharmaceutical companies pushing to sell on the market.²⁴⁸ Follow-on drugs, also called generic small-molecule drugs, have surely cut into brand-name drug revenue.²⁴⁹

C. *No Consensus on Exclusivity*

Each of the two pending bills appeal to either the innovative pharmaceutical industry or the generic pharmaceutical industry. Innovative and generic pharmaceutical companies have agreed that there is a need for follow-on biologics; however, they disagree about the exclusivity period for brand-name drugs.²⁵⁰ Generic companies favor shorter periods of exclusivity, approximately seven years, while innovative pharmaceutical companies support bills providing twelve to fourteen years of exclusivity.²⁵¹

Five congressional bills introduced in 2007 and 2008 began a thoughtful discussion regarding generic biologics, but they ultimately did not pass.²⁵² These bills would have amended

²⁴⁵ *Id.*

²⁴⁶ *Id.* at xiii.

²⁴⁷ *Id.* at xv.

²⁴⁸ *See id.*

²⁴⁹ Associated Press, *Brand Name Drugs Going Generic*, NBC ACTION NEWS.COM, Dec. 10, 2008, <http://www.nbcactionnews.com/mostpopular/story/Brand-Name-Drugs-Going-Generic/j5hwxTekPkSZG-NWWQ31MA.csp>. In the United States, generic prescription drugs cost approximately 1/3 less than brand name drugs. *Id.*

²⁵⁰ *See* Pollack, *supra* note 1.

²⁵¹ Donald Zuhn, *Top Stories of 2008: #9 to #6*, PATENT DOCS, Jan. 4, 2009, <http://www.patentdocs.org/2009/01/top-stories-of-2008-9-to-6.html>.

²⁵² H.R. 5629, 110th Cong. (2008); S. 1695, 110th Cong. (2007); S. 1505, 110th Cong. (2007); H.R. 1956, 110th Cong. (2007); H.R. 1038, 110th Cong. (2007).

section 351 of the PHS Act to establish a route for approval of an abbreviated biological product application for products that contain the same or similar active ingredients as previously licensed biological products.²⁵³

The Access to Life-Saving Medicine Act, House Bill 1038,²⁵⁴ was introduced February 14, 2007, by Representative Henry Waxman and stipulated that the biosimilar and reference must have the same mechanism of action for the same condition of use,²⁵⁵ but did not mention the provisions for data and market exclusivity.²⁵⁶ The Patent Protection and Innovative Biologic Medicines Act, House Bill 1956, was introduced April 19, 2007, by Representative Jay Inslee, and stated that biosimilar and reference material must merely show comparative results in health-related assays for the same dosage.²⁵⁷ House Bill 1956 took a bold move and provided twelve years of data exclusivity and just two years of market exclusivity.²⁵⁸ The Biologics Price Competition Innovation Act, Senate Bill 1695, was introduced on June 26, 2007, as a bipartisan effort guided by Senators Kennedy and Hatch, and suggested that the biosimilar and reference must have the identical route of administration, dosage form, and strength, as well as utilize the same mechanism of action for the same condition of use.²⁵⁹ The Biologics Price Competition Innovation Act, Senate Bill 1695, additionally called for four years of data exclusivity and eight years of market exclusivity.²⁶⁰ House Bill 5629, the Pathway for Biosimilars Act, would have provided four years of data exclusivity and eight years of market exclusivity. None of these bills, however, were passed in the 110th Congress.²⁶¹

²⁵³ *Id.*

²⁵⁴ H.R. 1038, 110th Cong. (2007).

²⁵⁵ *Id.* § 3(k)(1)(C).

²⁵⁶ *See* Zuhn, *supra* note 251.

²⁵⁷ H.R. 1956, 110th Cong. § 2(k)(5)(B) (2007).

²⁵⁸ *See* Zuhn, *supra* note 251.

²⁵⁹ S. 1695, 110th Cong. § 2(k)(2)(A)(i) (2007).

²⁶⁰ *Id.*; *see* Zuhn, *supra* note 251.

²⁶¹ *See supra* text accompanying note 252.

A Teva-funded study²⁶² suggested that an exclusivity period of seven years would be “sufficient for maintaining strong incentives to innovate while fostering a competitive marketplace.”²⁶³ Teva also questioned the need for exclusivity provisions that would add an additional seven to twelve years of protection.²⁶⁴ However, innovative companies have been supportive of bills that provide twelve to fourteen years of exclusivity.²⁶⁵ Thus, these studies illustrate the disconnect between innovative and generic companies regarding exclusivity periods.

D. A Professor’s View

Dr. Richard G. Frank, a leader in the field of health economics,²⁶⁶ has expressed that “the Hatch-Waxman framework is not sufficient to cover both relatively simple biopharmaceuticals and very large and complex molecules—a new regulatory framework is needed.”²⁶⁷ While he acknowledges that the loss of patent protection increases the urgency for regulatory policy promoting price competition and preserving the safety and efficacy standards,²⁶⁸ he states that the FDA should receive a “great deal of discretion” in making multifaceted, situation-specific judgments.²⁶⁹ Thus, “the conflicting goals of bolstering price competition in biopharmaceutical markets and preserving for a nuanced policy that must be based on the best science and key features of the current economics of biopharmaceutical markets—not on the impassioned claims of the interested parties,”²⁷⁰ create a difficult set of parameters that requires situation-specific balancing.

²⁶² Teva is a leading company that specializes in follow-on drugs. Posting of Elysa Brooke Goldberg, Ph.D. to IPLJ Law Blog, <http://iplj.net/blog/archives/381> (Apr. 14, 2009).

²⁶³ ALEX M. BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS 3 (2008), available at http://www.tevad.com/Brill_Exclusivity_in_Biogenics.pdf.

²⁶⁴ See generally *id.*

²⁶⁵ See *id.* at 6 (discussing Eshoo Bill).

²⁶⁶ Richard G. Frank, Ph.D., *Regulation of Follow-On Biologics*, 357 NEW ENG. J. MED. 841, 843 (2007), available at <http://content.nejm.org/cgi/content/short/357/9/841>.

²⁶⁷ *Id.*

²⁶⁸ *Id.*

²⁶⁹ *Id.*

²⁷⁰ *Id.*

Dr. Frank interestingly advocates giving the FDA the discretion to permit generic biologics, instead of problematically simplifying the approval process via the Hatch-Waxman Act.²⁷¹ Dr. Frank hypothesizes that if the FDA were to require clinical studies of generic biologics, then the health of the community would be a top priority.²⁷² In contrast, he believes that if the bioequivalence of the complex protein structures were the main deciding factor alone, the activity of the protein would not be considered.²⁷³ In this way, clinical trials would examine how effective the follow-on biologic is and be able to compare the biologic's strength to the original brand-name biologic.²⁷⁴

E. Comparing a Patient's and a Doctor's View

Thus far, the analysis of this paper addresses *if* the generics will be permitted to compete with brand-name pharmaceutical biologics using today's legislation. Another question to complicate the story is: *will* doctors prescribe the potential biosimilar in place of the innovative biologic? Doctors who do not feel comfortable substituting the generic for the brand-name biologic could disarm the entrance of biosimilars into the market.²⁷⁵

Data strongly suggests that both doctors and patients harbor brand loyalties.²⁷⁶ Many studies analyze patients' choice to purchase brand-name pharmaceuticals instead of generic equivalents.²⁷⁷ One theory is that patients believe generic drugs,

²⁷¹ *Id.*

²⁷² *Id.*

²⁷³ *See id.*

²⁷⁴ Corbitt, *supra* note 7, at 388.

²⁷⁵ *See* GOV'T ACCOUNTABILITY OFFICE, PRESCRIPTION DRUGS: IMPROVEMENT NEEDED IN FDA'S OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING 1-4 (2006), *available at* <http://www.gao.gov/new.items/d0754.pdf> (noting the increase in Direct-to-Consumer ("DTC") advertising since 1997 and the implications of this trend for medical professionals).

²⁷⁶ William H. Shrank, Emily R. Cox, Michael A. Fischer, Jyotsna Mehta & Niteesh K. Chaudhry, *Patients' Perceptions of Generic Medications*, 28 HEALTH AFFAIRS 546, 546 (2009) (reporting results from a study sample regarding patients' perceptions about generic drug substitutions).

²⁷⁷ *Id.*

priced lower than brand-name drugs, are of inferior quality.²⁷⁸ A telling study performed in 2000 found that “[t]he percentage of respondents who perceived that generic prescription drugs were riskier than brand name products varied from 14.2% to 53.8%, depending on the medical condition being treated.”²⁷⁹ In 2005, another study found that “37% of patients expressed general skepticism towards generic drugs because of their lower price.”²⁸⁰ Therefore, many patients ultimately decide against the benefit of savings offered by generic drugs and instead pay higher prices for brand-name drugs.²⁸¹

When faced with the decision to prescribe generics over name-brand pharmaceuticals, physicians conduct themselves similarly to patients.²⁸² One theory is that physicians tend to be risk-averse and would prefer not creating variability in patient treatment.²⁸³ Physicians have long been criticized as being “creatures of habit.”²⁸⁴ Such character traits make it difficult to prescribe generic drugs. However, such caution is well founded. Organic chemistry has shown that “polymorphism” frequently occurs when generating drugs.²⁸⁵ Polymorphism is the ability of drugs to exist in many different types of crystalline phases, all having different reactivity.²⁸⁶ FDA scientists know that such a cocktail of different crystalline phases can affect drug stability and drug activity.²⁸⁷

²⁷⁸ Rebecca Ruiz, *What You Should Know About Generic Drugs*, FORBES, July 27, 2009, <http://www.forbes.com/2009/07/27/generic-drugs-prescriptions-lifestyle-health-drugs.html>.

²⁷⁹ Julie M. Ganther & David H. Kreling, *Consumer Perceptions of Risk and Required Cost Savings for Generic Prescription Drugs*, 40 J. AM. PHARM. ASS'N 378, 378 (2000).

²⁸⁰ W. Himmel et al., *What Do Primary Care Patients Think About Generic Drugs?*, 43 INT'L J. CLINICAL PHARMACOLOGY & THERAPEUTICS 472, 472 (2005).

²⁸¹ *Id.*

²⁸² *See id.* at 477 (“[P]atients as well as physicians do not have the incentive to invest in low-cost treatment as long as insurance companies pay the costs of prescription, regardless of their generic or brand-name status.”).

²⁸³ F.M. Scherer, *Pricing, Profits, and Technological Progress in the Pharmaceutical Industry*, 7 J. ECON. PERSP. 97, 101 (1993).

²⁸⁴ *Id.*

²⁸⁵ Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications, http://www.fda.gov/ohrms/dockets/ac/02/briefing/3900B1_04_Polymorphism.htm (last visited Aug. 30, 2009).

²⁸⁶ *Id.*

²⁸⁷ *Id.*

Thus, physicians have good reason to question the ability of generic drugs to perform comparably to brand-name pharmaceuticals.

While in theory an active ingredient has the same function and potency regardless of being brand-name or generic, it is ultimately the patient that needs to determine if the small molecule is acting identically. Many patients have noted that they can identify differences in the potency of brand-name versus generic drugs.²⁸⁸

Because patients question the quality of generic drugs and physicians err on the side of caution, more brand-name drugs are routinely prescribed instead of an identical authorized generic to avoid potential tort liability.²⁸⁹ The fact that generics are poorly regarded in a percentage of the medical field and in society raises the question of whether doctors would substitute for and patients would request follow-on biologics for brand-name biologics.²⁹⁰

On behalf of the innovative brand-name pharmaceutical companies, the Biotechnology Industry Organization (BIO) is concerned about doctors being stripped of choice.²⁹¹ The Waxman Bill will permit biosimilars to be substituted for the innovative biologic without the intervention of the prescribing doctor.²⁹² The generic biologic may be permitted as a substitute without the doctor's approval, which could ultimately limit the doctor's control and treatment of the patient.

²⁸⁸ See Road Back Foundation, Are Generic Drugs as Effective as Brand Name?—Not Always!, http://www.roadback.org/index.cfm/fuseaction/education.display/display_id/120.html (last visited Aug. 30, 2009).

²⁸⁹ Thomas Chen, *Authorized Generics: A Prescription for Hatch-Waxman Reform*, 93 VA. L. REV. 459, 477 (2007).

²⁹⁰ *Id.*

²⁹¹ See BIO, *supra* note 24.

²⁹² Jonathan Sheffi, What Are Follow-On Biologics? Will They Really Save Us Billions of Dollars?, *The Soul of Biotech* (June 29, 2009), <http://www.thesoulofbiotech.com/2009/06/29/what-are-follow-on-biologics-will-they-really-save-us-billions-of-dollars/>.

F. Brand-Name Perspective: Impossibility of Duplication and the Question of Patentability

Although patent protection is available for biologics in many circumstances, there may be a limited scope of protection.²⁹³ The patent system further regulates competition in the biologics market, as there may be restrictions on the availability of proprietary rights in biological substances.²⁹⁴ The 110th Congress reviewed legislation²⁹⁵ that would permit an expedited marketing approval pathway.²⁹⁶ The Access to Life-Saving Medicine Act, House Bill 1038 and Senate Bill 623, would have permitted the Secretary of Health and Human Services to monitor what studies were necessary to establish comparability.²⁹⁷ Comparable biologics would be necessary to maintain the same chemical reaction, the same mechanism of performing this reaction, as well as the same dosage form, strength, etc.²⁹⁸ While the identical chemical reaction and mechanism for reaction would be relatively easy to prove, the same dosage form and strength could be very tricky to establish.²⁹⁹ If all of these parameters were to be met, then the generic form of the brand-name biologic would be deemed “interchangeable.”³⁰⁰ An interchangeable product would be required to produce the same clinical results as the brand-name innovative drug.³⁰¹

There is a formidable lobby, lead by the Intellectual Property Owners Association, against approval of follow-on biologics, which strongly asserts that it is impossible to replicate a brand-name pharmaceutical’s biological innovations exactly, due to

²⁹³ WENDY H. SCHACHT & JOHN R. THOMAS, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 2 (2008), available at https://www.policyarchive.org/bitstream/handle/10207/3161/RL33901_20070305.pdf.

²⁹⁴ *Id.*

²⁹⁵ See *supra* notes 252–61 and accompanying text.

²⁹⁶ See *supra* Part III.C.

²⁹⁷ S. 623, 110th Cong. (2007); H.R. 1038, 110th Cong. (2007).

²⁹⁸ S. 623, 110th Cong. (2007); H.R. 1038, 110th Cong. (2007).

²⁹⁹ See *supra* note 93.

³⁰⁰ See *supra* note 93.

³⁰¹ See *supra* note 93.

technological limitations.³⁰² The crux of this argument lies in health and safety concerns, and proponents of this view advocate against an accelerated approval process for follow-on biologics.³⁰³ These pharmaceutical companies assert that an end product is unpredictable, even with guidance through patent disclosures, including deposited biological samples.³⁰⁴ This argument stipulates that since it is impossible to recreate the innovative biologic perfectly, patent protection should not apply.³⁰⁵

While the safety and health of patients is a strong aspect of this argument, considering only safety and health undercuts the patentability of the biologic. Enablement is a fundamental step in securing patentability.³⁰⁶ If it is impossible to replicate the patented invention, then there is a prima facie case against patenting the invention due to non-enablement.³⁰⁷ Using the inability to fulfill the enablement requirement as an argument weakens incentives to patent inventions and is unfair. If brand-name pharmaceuticals were unable to be patented, companies would instead use the power of trade secrets to insulate them from competition.³⁰⁸ Protecting brand-name pharmaceuticals through trade secrets would drive down the amount of information available to any pharmaceutical company regarding any type of technique.³⁰⁹ Consequently, it would be more unlikely that

³⁰² Letter from Herbert C. Wamsley, Executive Director, Intellectual Property Owners Association, to Anna Eshoo, U.S. H. Rep. (July 17, 2009), available at http://www.ipo.org/AM/Template.cfm?Section=Board_Resolutions_and_Position_Statements&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=23296 (memorializing the IPO's support for House Bill 1548).

³⁰³ Donald Zuhn, *IPO Passes Resolution on Biosimilars*, PATENT DOCS, Sept. 23, 2008 <http://www.patentdocs.org/2008/09/follow-on-biolo.html>.

³⁰⁴ Corbitt, *supra* note 7, at 397.

³⁰⁵ See Stephen B. Judlowe & Brian P. Murphy, *IP VALUE 2005, Proposed Legislation for Follow-On Biologic Pharmaceuticals in the US*, http://www.buildingipvalue.com/05_NA/135_138.htm.

³⁰⁶ 35 U.S.C. § 112 (2006). For a description of the enablement requirement, see United States Patent and Trademark Office, *The Enablement Requirement*, http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2164.htm (last visited on Oct. 14, 2009) [hereinafter *The Enablement Requirement*].

³⁰⁷ See *The Enablement Requirement*, *supra* note 306.

³⁰⁸ Corbitt, *supra* note 7, at 398.

³⁰⁹ See *id.*

competitors would be able to manufacture follow-on biologics.³¹⁰ Additionally, reverse-engineering would be nearly impossible, so trade secrets would be a workable way to protect such intellectual property. If inventions and innovations were protected by trade secret and not patent law, generic equivalents would be impossible to generate unless the secrets, for example, were sold.

A major flaw with not extending patentability to innovations that are very difficult to reproduce is that the innovators no longer have the protection of a patent. Losing the availability of patent rights could very likely be a large disincentive to continue funding pharmaceutical companies and their research and development efforts. The rights of patents extend from literal infringement through the doctrine of equivalence (“DOE”).³¹¹ The DOE is only available to patented products, not to those covered via trade secret because patented innovations are extended protections that trade secrets are not.³¹² The DOE allows a court to hold a party liable for patent infringement for an equivalent to the claimed invention.³¹³ Courts may use the DOE to stop companies from avoiding infringing patents by making insubstantial changes to the innovation.³¹⁴ Without the DOE, the value of patents “would be greatly diminished.”³¹⁵

³¹⁰ *Id.* (“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.”).

³¹¹ See ROBERT P. MERGES, PETER S. MENELL & MARK A. LEMLEY, *INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE* 263–64 (4th ed. 2006) (describing how the doctrine of equivalents expands on patent protection against literal infringement).

³¹² United States Patent and Trademark Office, General Information Concerning Patents, <http://www.uspto.gov/go/pac/doc/general/#nature> (last visited Sept. 27, 2009) (stating that patent protection refers to the right to exclude others from making, using, offering for sale or selling or importing the invention).

³¹³ *Royal Typewriter Co. v. Remington Rand, Inc.*, 168 F.2d 691, 692 (2d Cir. 1948).

³¹⁴ *Id.*

³¹⁵ *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002).

III. COME TOGETHER: THE UNITED STATES SHOULD MAINTAIN THE CURRENT BALANCE INHERENT IN PATENT LAW AND NOT SACRIFICE HEALTH FOR SPEEDY PRICE COMPETITION

Congress should implement key changes to the Hatch-Waxman Act to monitor and address the primary concern of health. While Congress has written and evaluated many bills, it has not found a solution that opposing sides can agree upon. It is imperative that the urgency of supplying cheaper biologics does not supersede the requirement for safe and effective medication. The long-term goal is for innovative research to maintain incentives to bring life-saving biologics to Americans; without this incentive, Americans will ultimately be the losers.

A. *The Lines of Communication Are Open*

A passable bill “should adequately compensate generic manufacturers by providing at least some exclusivity for biologic products.”³¹⁶ All of the proposed Congressional bills had drawbacks, either because they had too much exclusivity (House Bill 1038 and Senate Bill 1695) or did not have any (House Bill 1956),³¹⁷ and consequently, these bills were not passed.³¹⁸ Until there is a thoughtful conversation between both of these approaches, the innovative pharmaceutical companies will enjoy a market without competition from follow-on biologics.³¹⁹ Considering that both innovative and generic pharmaceutical companies have an interest in maximizing gross revenue, it is encouraging that a thoughtful bipartisan discussion has already ensued via the 110th Congress.³²⁰

The writers of the Eshoo Bill have considered many points of contention from the previous 110th Congress and have softened

³¹⁶ Kelleher, *supra* note 43, at 262.

³¹⁷ See *supra* text accompanying notes 252–61.

³¹⁸ See *supra* text accompanying note 262.

³¹⁹ See Waxman, *supra* note 137.

³²⁰ Orrin G. Hatch, U.S. Sen., Now is the Time to Act: The Urgent Need to Pass S. 1695 in the 110th Congress (Sept. 22, 2008), <http://www.biosimilarstoday.com/2008/Hatch.pdf>.

the bill's stance accordingly.³²¹ An interesting twist in the Eshoo Bill is that experimentation is not required, as this bill states that it could be waived.³²² It seems as though the 110th Congress's struggle with this issue can be shelved because of this concession. The most hotly contested issue of the upcoming 111th Congress will be the exclusivity provision.³²³ There is a large discrepancy between five or twelve years of exclusivity, and negotiation to reach a term will not be easy. The longer term of exclusivity provides the ability for follow-on biologic companies to follow through with additional experimentation,³²⁴ a possibility that would not exist if the five-year exclusivity term were adopted. Thus, the writers of the Eshoo Bill have already taken into consideration the lessons of the 110th Congress and have made the concession of mandatory experimentation. Any additional concession of the Eshoo Bill, specifically the exclusivity of innovative biologics, would drastically undermine consumer safety.

B. Consumer Safety

Generic pharmaceutical companies' strong interest in creating affordable biologics can be one-sided, in both the short and long-term. By not being subject to the standard testing procedures, the follow-on biologic could adversely affect patients.³²⁵ Thus, by not requiring additional experimentation, we are undermining the public's need for safe medicine. Additionally, innovative companies producing these pioneer biologics would not profit

³²¹ Kurt R. Karst, FDA Law Blog, Rep Eshoo Proposes Draft Biogenics Bill (Feb. 18, 2000), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/03/rep-eshoo-introduces-followon-biologics-bill-proposed-pathway-for-biosimilars-act-is-reportedly-simi.html. Rep. Anna Eshoo (D-CA), Rep. Jay Inslee (D-WA) and Rep. Joe Barton (R-TX) are the authors of the Eshoo Bill.

³²² Karst, *supra* note 321.

³²³ See *supra* note 251 and accompanying text.

³²⁴ See *supra* text accompanying notes 209–14.

³²⁵ See Corbitt, *supra* note 7, at 397–98 (“Executives from large pharmaceutical corporations . . . 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.”).

nearly as much as they would have in the past.³²⁶ As a result, those companies will have less incentive to invest in cutting-edge research to develop new, potentially life-saving medicines.³²⁷ If Congress does not strike a balance between innovative and follow-on biologics, then the public is at risk to receive dangerous follow-on biologics, and innovative pharmaceutical companies will not have the resources to invest into research and development.

Considering that both the Waxman Bill and Eshoo Bill have compromised on the requirement of additional experimentation for follow-on biologics, exclusivity is the next obvious issue of contention. Since companies generating follow-on biologics would be able to cut years off of the process of getting biologic products to store shelves,³²⁸ these companies would surely want shorter periods of innovative drug exclusivity. A short five-year period of exclusivity is not desirable because it would undermine the possibility of additional experimentation that the Eshoo Bill provides.³²⁹ A longer period of exclusivity is crucial, as the Eshoo Bill suggests, because this Bill innately provides additional time for the follow-on manufacturer to test its biological product. In this way, Congress can better achieve consumer health and safety in both the short and long-term.

C. Preservation of Incentives for Innovative Drug Companies

An underlying priority must be to promote continued research and development in the fields of biotechnology. Thus, American patents must be strong and reliable, protecting the intellectual property that they breed. If American patents are not as strong as foreign patents or if there is significant uncertainty as to how

³²⁶ See *id.* at 390–91 (proposing that production of biosimilars may not be economically efficient because its development costs are much higher than the development costs of a small-molecule generic); see also Scherer, *supra* note 283, at 103–06 (“[M]ost [new products] achieve much lower sales. . . . [N]ew drug development resembles a risky lottery that throws out rich rewards to a few big winners while the majority of entries lose money.”).

³²⁷ Corbitt, *supra* note 7, at 390–91.

³²⁸ Press Release, Federal Trade Commission, FTC Releases Report on “Follow-on Biologic Drug Competition” (June 10, 2009), <http://www.ftc.gov/opa/2009/06/biologics.shtm>.

³²⁹ H.R. 1427, 111th Cong. (2009).

inventors will interpret American patents, inventors will quickly lose incentive to continue filing in the United States. Thus, protecting innovation by approving patents for biologics is mandatory for continued industry and research growth.³³⁰

The example of insulin³³¹ highlights why patent protection is so important for biological research, as it took almost twenty years for Eli Lilly to purify insulin and successfully obtain approval to market this therapy.³³² If the leaders within Eli Lilly knew that their purified insulin would ultimately never receive patent protection, they may not have invested almost two decades of research in this field. Additionally, Eli Lilly may not have pursued purification of naturally occurring biological proteins if their patent rights were abbreviated and if they knew that generics would immediately compete with their twenty years of hard work and investment.

A final issue that needs to be addressed is whether abbreviating the period of patent protection is an unconstitutional taking without just compensation.³³³ Permitting pharmaceutical companies manufacturing generics to take and use the discoveries of innovative pharmaceuticals presents a strong argument for an unconstitutional taking.³³⁴ Considering that huge amounts of money are invested by brand-name pharmaceuticals for research and development, there needs to be some reasonable compensation for the discoveries.

CONCLUSION

The Biologics Act of 2007 first attempted to mold the Hatch-Waxman Act into a vehicle previously encompassing tiny, simple drugs into an extension for large, complex biological molecules.³³⁵

³³⁰ Corbitt, *supra* note 7, at 400.

³³¹ “Deducing the steps required to purify and produce insulin, for example, took considerable work by some of the top scientists in the field.” *Id.* at 402.

³³² *Id.*

³³³ *Id.*

³³⁴ See *Monsanto Co. v. Acting Admin. U.S. EPA*, 564 F. Supp. 552, 566–67 (E.D. Mo. 1983) (holding that the government attempted an unconstitutional taking of an innovator manufacturer’s property right when requiring information held in trade secret).

³³⁵ See *supra* text accompanying notes 137–44.

However, the question remains whether applying the Biosimilars Act to the established Hatch-Waxman process of approval and generic manufacture would be beneficial. The past and current bills seek that generic biologics manufacturers satisfy further requirements, such as conducting extensive clinical studies, which will increase the biosimilar's costs and decrease the margin between the price of the innovative biologic and the follow-on generic.³³⁶ Both bills have been referred to the House Energy and Commerce Committee and the House Judiciary Committee.³³⁷

An additional concern, besides higher manufacturing costs and decreased profits, is the actual market for follow-on biologics. Doctors and patients alike have reservations about using generic drugs in place of brand-name drugs. There is no way to predict how follow-on biologics will be accepted by the general public; will follow-on biologics be embraced as cheaper alternatives, or will they be rejected because of potential health concerns? Passing the Eshoo Bill or the Waxman Bill will answer this lingering question. Because of these concerns, it is unclear whether the follow-on biologic market will be as robust a competitor as the generic small-molecule market. Clearly, if a follow-on biologic market broadens due to the passing of the Biologics Act, it is of the utmost importance that these generic biological medicines are safe for consumer use. Therefore, it is in the best interest of consumers to demand experimentation. Experimentation requires time, and the Eshoo Bill provides this needed time. The Eshoo Bill carefully and clearly lays out the regulation of biosimilars, additionally leaving room for variation in experimentation requirements. The Eshoo Bill best anticipates the needs of the American people and must be voted for in the upcoming 111th Congress.

³³⁶ See *supra* notes 195–216 and accompanying text; see also H.R. 1427, 111th Cong. (2009).

³³⁷ H.R. 1548, 111th Cong. (2009).