
October 2015

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Recommended Citation

Jessica R. Underwood, *What the EU Has That the U.S. Wants: An Analysis of Potential Regulatory Systems for Follow-on Biologics in the United States*, 10 DePaul J. Health Care L. 419 (2007)
Available at: <https://via.library.depaul.edu/jhcl/vol10/iss3/5>

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WHAT THE EU HAS THAT THE U.S. WANTS: AN ANALYSIS OF POTENTIAL REGULATORY SYSTEMS FOR FOLLOW-ON BIOLOGICS IN THE UNITED STATES

Jessica R. Underwood¹

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¹ The author would like to thank Dr. Manfred Laubichler and Dr. Jane Maienschein for their comments and support during the writing and editing of this paper. Additionally, the author would like to thank Espicom for its research contributions during the completion of this article.

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INTRODUCTION

In March 2004, the European Commission denied approval for the world's first generic biologic, Sandoz's human growth hormone Omnitrope,² which likely reinforced the U.S. Food and Drug Administration's ("FDA") general skepticism toward biogeneric drugs at the time. Not surprisingly, in September 2004, the FDA also rejected the drug, stating that it was unable to reach a decision due to uncertainty regarding scientific and legal issues.³ The European Union's ("EU") rejection of Omnitrope was a surprise, however, because the EU had passed legislation in 2003 allowing companies to apply for permission to sell generic biologics⁴ and, in 2004, released guidance regarding how to demonstrate similarity between generic and brand-name products.⁵ Nonetheless, on January 27, 2006, the European Medicines Agency ("EMA") gave Omnitrope the green light when it announced that the biogeneric's studies showed comparable quality, safety, and efficacy to its brand name product, bringing the EU one step closer to full-fledged regulatory approval for follow-on

² Edward Winnick, *EU Turns Down Biotech Generic*, THE SCIENTIST, Apr. 8, 2004, <http://www.the-scientist.com/news/20040408/03> (last visited Jan. 5, 2007).

³ Susan J. Ainsworth, *Biopharmaceuticals*, CHEM. & ENG. NEWS, June 6, 2005, at 23.

⁴ Alison Langley, *Engineered Drugs Open New Issue of Regulation as Patents Expire*, N.Y. TIMES, Aug. 9, 2003, at A6.

⁵ ESPICOM, BIOGENERIC 2005: AN EMERGING GLOBAL MARKET? 44 (2d ed. 2005).

biologics.⁶ Meanwhile, the United States remains at a stand still: not only is no regulatory system in place, but also, more importantly, there is an industry-wide debate regarding whether a regulatory system can even be created or implemented at all.

Recently, the world's first biopharmaceuticals, which include many of the most expensive drugs, have begun to lose patent protection.⁷ Although the world market for generic biologics was virtually nonexistent in 2004,⁸ it is expected to become a \$5.4 billion industry by 2008, if favorable regulatory systems are put into place.⁹ Generic biotechnology firms have lobbied for a favorable regulatory environment for these products, taking the pro-consumer position that health care costs must be minimized.¹⁰ This position is or should be firmly supported by the American public, who save an estimated \$8 to \$10 billion a year on generic drugs at retail pharmacies.¹¹ On the other hand, brand-name drug companies have fought to block generic competition, citing both safety and regulatory concerns as insurmountable roadblocks.¹²

On a practical level, this debate affects more than just pharmaceutical companies' bottom line. Whether generic drugs become available and, in turn, their level of safety and efficacy will have a tremendous impact on Americans' quality of life and, in some cases, mean the difference between life and death. Although prescription drugs make up only ten percent of health care spending in America, drug prices are the most rapidly increasing component of the entire health care system.¹³ United States law prevents the government

⁶ Tom Wright, *EU Agency Backs Generic Growth Hormone*, INT'L HERALD TRIB., Jan. 27, 2006, <http://www.iht.com/articles/2006/01/27/business/drug.php>. This should pave the way for the European Commission, the executive arm of the EU, to give formal authorization to Omnitrope within a few months. *Id.*

⁷ Ainsworth, *supra* note 3, at 21.

⁸ *Id.*

⁹ *Id.*

¹⁰ *Id.* at 22.

¹¹ CDER's Office of Generic Drugs (CDER), *Organizational Components*, <http://www.fda.gov/cder/ogd/#Introduction> (last visited Jan. 5, 2007).

¹² Ainsworth, *supra* note 3, at 22.

¹³ Henry J. Kaiser Family Foundation, *Trends and Indicators in the Changing Health Care Marketplace*, 2004 UPDATE, Apr. 2004. In a study of Medicare and Medicaid data from 1992-2002, the Kaiser Foundation estimated a 16.5% increase in spending on prescription medications each year. *Id.*

from negotiating lower prices with drug companies,¹⁴ which would alleviate this problem.¹⁵ While the introduction of generics would reduce the price of these medicines by twenty-five to seventy-five percent, the savings to the health care system would be significantly more because biologics are some of America's most expensive drugs.¹⁶

Seniors as a group are likely to be more affected than other groups by high health care costs because of their fixed incomes and dependency on Medicare. In 2005, seniors were expected to spend thirty-seven percent of their social security check on health care costs, and these estimates are expected to rise to forty percent in 2011 and fifty percent in 2021.¹⁷ The new Medicare drug benefit program beginning in 2006, which attempts to save money on drug costs, is not only voluntary, but also requires a \$420 premium per year with substantial co-payments.¹⁸ Unless Congress takes action to hold down health care costs for seniors, official projections indicate that health care costs alone will consume Social Security benefits by the time today's generation reaches retirement.¹⁹ The introduction of generic biologics into the U.S. market would be an effective solution to alleviate high drug costs for Medicare recipients.

Employers are another group hurting from high health care costs, which effectively decreases profits and increases incentives to outsource overseas. For example, in the past two years, General Motors spent \$9.3 billion on health care benefits for current and former employees.²⁰ The company expects to spend a shocking \$63 billion on

¹⁴ William M. Welch, *Medical Costs Eat at Social Security*, USA TODAY, Sep. 14, 2004, http://www.usatoday.com/news/washington/2004-09-13-medicare-costs_x.htm (last visited Jan. 5, 2007).

¹⁵ See, e.g., Alex Berenson, *A Cancer Drug's Big Price Rise Is Cause for Concern*, N.Y. TIMES, Mar. 12, 2006. See also Paul Wallace, *The Health of Nations*, ECONOMIST, July 17, 2004 (reporting that prescription drugs in the United States are much more expensive than in Canada or Europe where government controlled health-care systems can negotiate bigger discounts).

¹⁶ Stephan Herrera, *Biogenerics Standoff*, 22 NATURE BIOTECHNOLOGY 1343, 1343 Nov. 2004.

¹⁷ 2004 Medicare Trustees Report, *SMI Out of Pocket Expenses as Percentage of Illustrative Social Security Benefit*, http://www.house.gov/stark/news/108th/news_2004-09-14_MedPremDoc.htm (last visited Jan. 5, 2007). These expenditures include Medicare premiums, co-payments, and out-of-pocket expenses. *Id.*

¹⁸ Welch, *supra* note 14.

¹⁹ *Id.*

²⁰ Herrera, *supra* note 16, at 1343.

health care in the coming decades.²¹ On the other hand, Japan-based Toyota spends less than American car companies on health care benefits because Japan, similar to Europe and Canada, has health care programs with price-controlled drugs.²² Instead of negotiating lower prices with drug companies, a step the American government has thus far been unwilling to take, the availability of generic biologics would provide immediate relief to this growing problem for employers.

The current biogeneric stand still in the United States also has the potential to detrimentally affect other countries as well. Some international agencies assert that each day without biogenerics negatively impacts the health of people worldwide who cannot afford these drugs otherwise.²³ According to the World Health Organization initiative, the most effective way to produce and stockpile the amount of medication required to treat the 24.5 million people in Africa with HIV²⁴ would be to embrace biogeneric manufacturers.²⁵ International agencies have asserted that the FDA's strict standard for bioequivalence is needlessly high, which forces biogeneric drugs to be removed from the international market and, as a result, results in needless deaths.²⁶ These agencies assert that a lower standard for bioequivalence would result in the availability of more biogenerics to treat more HIV patients and also collaterally reduce the rates of HIV transmission in the affected areas.²⁷

²¹ *Id.* (citing Danny Hakim, *Carmakers in For a Long Haul in Paying for Retiree Health Care*, N.Y. TIMES, Sep. 14, 2004, at 1).

²² Herrera, *supra* note 16, at 1343.

²³ Mark Wainberg, *Generic HIV Drugs – Enlightened Policy for Global Health*, 352(8) J. AM. MED. ASS'N, Feb. 24, 2005, at 1, available at <http://www.cptech.org/ip/health/generic/wainberg02242005.html> (last visited Jan. 5, 2007). See also William F. Haddad, *Epidemics and the Generic Medicines Industry*, X(2) BROWN J. WORLD AFF. 213, 223 (Winter/Spring 2004) (arguing that similar to the introduction of chemical generic drugs, the controversy surrounding the implementation of generic biologics is largely political, not scientific).

²⁴ There were an estimated 24.5 million people requiring HIV therapy in 2005. Avert.org, *How Many People in Africa Are Infected with HIV?*, <http://www.avert.org/aafrica.htm> (last visited Jan. 5, 2007).

²⁵ Wainberg, *supra* note 23.

²⁶ *Id.*

²⁷ *Id.* The rates of transmission would be reduced because high viral loads are the strongest corollary to transmission of HIV. *Id.* In other words, with more people being treated for HIV, viral loads would be lower, which would decrease the likelihood of transmission. See *id.* Further, antiretroviral drugs significantly reduce HIV levels in plasma & the viral burden in fluids such as semen, which would also reduce transmission rates. *Id.*

Regardless of the benefits that the introduction of biogenics could potentially unleash, there are substantial safety and efficacy concerns that innovator manufacturers and the FDA posit as real threats. The concern is that the premature introduction of generic biologics into the market would cost some Americans their lives because biologics are too complex to be copied with the current technology, which cannot accurately identify crucial changes in the proteins.²⁸ Further, for many of these protein products, there are no analogous animal models that can be used for predictive value.²⁹ As a result, it is impossible to determine how changes in the biogeneric will affect the population at large.³⁰ Without any hard evidence to the contrary, this point is difficult to refute.³¹

While the United States resolves this internal debate, biogeneric companies have targeted countries with more lax regulatory barriers and less intellectual property protection. This tactic allows these manufacturers to gain experience in manufacturing and sales early on before eventually expanding into the more lucrative western market.³² In addition to cheaper manufacturing costs,³³ this head start, so to speak, allows these producers to earn a return on their investment while refining their capabilities--advantages that "wait-and-see players" do not have.³⁴ On the other hand, the introduction of biogenics into these countries may raise extensive bioethical concerns regarding safety and efficacy relative to socioeconomics as these drugs may pose serious threats to recipients' health.³⁵ Nonetheless, whether this issue

²⁸ See Herrera, *supra* note 16, at 1343.

²⁹ Letter from Sara Radcliffe, Managing Director of BIO, to Susana Maria Soobhujhun, European Medicines Agency (Feb. 28, 2005), at 2, *available at* <http://www.bio.org/reg/20050228.pdf> (last visited Jan. 5, 2007).

³⁰ *Id.* at 2.

³¹ See Herrera, *supra* note 16, at 1343.

³² Dr. Hajimu Morioka, *Considerations About Generic Biologics*, PHARMOGENERICS, Dec. 1, 2005, at 26, *available at* <http://www.touchbriefings.com/pdf/955/ACFB481.pdf>. Morioka (last visited Jan. 5, 2007).

³³ For example, during the Soviet era, a Ukrainian biological research institute developed a sophisticated form of bacteriophage technology. *Id.* at 29. U.S. companies have partnered with this institute to produce biologics such as interferon at one-tenth of the cost of current methods. *Id.*

³⁴ Ainsworth, *supra* note 3, at 24.

³⁵ *Cf.* Wainberg, *supra* note 23, at 2 (rejecting the assertion that introducing generic biologics into less strictly regulated countries should rouse bioethical or immoral concerns. Wainberg argues these types of arguments will only serve to deny millions of people lifesaving drugs and deny the world greater access to public health benefits).

goes more toward the countries' own governmental and regulatory structures or falls to the generic companies or the international community remains debatable.

Unfortunately, innovator and generic companies have positioned themselves on extreme sides of the debate, which has effectively stymied the implementation of any type of biogeneric pathway. Although it has had nearly twenty years to prepare for this,³⁶ the FDA has failed to act and is being pulled from both sides. The more quickly the FDA implements a method for regulating generic biologics and a standard for determining bioequivalence, the more quickly reduced drug costs will go into effect. Consequently, significantly reduced drug costs would alleviate an overburdened and dragging health care system, which would in turn improve the American economy and the health, quality of life, and lifespan of people worldwide. But before this can happen, the FDA and Congress must decide which side has the better argument, and how much they are willing to risk to help the bottom line.

Part I of this article explores the extreme sides of the debate between innovator and generic manufacturers and the arguments supporting each side's position. Part II briefly reviews the United States's current regulatory systems and abbreviated pathways for both drugs and biologics in order to evaluate which pathway would be most effective for generic biologics. Part III examines the regulatory measures for generic biologics that the EU has adopted. Finally, Part IV analyzes the potential regulatory pathways for biogenerics in the United States and makes suggestions, in light of the EU's progress, to facilitate the implementation of such a pathway in the United States.

I. EXTREME SIDES OF THE DEBATE: INNOVATOR V. GENERIC ARGUMENTS³⁷

Proponents and advocates of a regulatory pathway for generic biologics are sharply divided across industry lines, primarily by generic and brand-name interests. Nonetheless, the FDA and Congress will

³⁶ See Herrera, *supra* note 16, at 1343.

³⁷ It should be noted that this classification is becoming less one-sided, as some innovator companies are recently preparing to enter the generic biologic market. See generally Val Brickates Kennedy, *Pfizer Eyes Generic Biologics Market*, MARKETWATCH, <http://www.marketwatch.com/news/story/pfizer-eyes-generic-biologics-market/story.aspx?guid=%7B13CC469B-AE9C-4137-8B48-E832E57896CF%7D> (last visited Jan. 5, 2007).

ultimately come down somewhere in the middle. To do this, Congress must balance the incentives for both brand-name and generic drug firms.³⁸ While an abbreviated approval system for generic biologics must be implemented to make them more affordable and available to the public, the intellectual property rights of research-based firms must also be respected to preserve the financial incentives that innovator firms have to develop new products.³⁹

A. Innovator Manufacturers' Interests

At the extreme, many in the biotechnology industry argue that the creation of a fast track approval process for generic biologics is the worst nightmare of an inherently risky industry that is already struggling to attract the necessary capital to bring new products to the market.⁴⁰ This side argues that current technology makes it difficult to identify changes in the proteins and, thus, impossible to determine how these changes will affect clinical results.⁴¹ Although physical and chemical tests exist to determine the similarity between small-molecule generic and innovator biologics, this side argues that these tests are not scientifically relevant or sufficiently predictive to analyze these protein products.⁴² Because biologics have convoluted chemical structures that are produced in humans, animals, plants, and microorganisms, these products require more extensive processing, purification, and stabilization.⁴³ Furthermore, for many of these proteins, according to

³⁸ *The Law of Biologic Medicine: Hearing Before the Subcomm. on the Judiciary, 108th Cong. 1, 3 (2004)* [hereinafter *Biologic Medicine Hearing*] (statement of Sen. Orrin Hatch, Chairman, Subcomm. on the Judiciary).

³⁹ *Id.*; see also *Biologic Medicine Hearing, supra* note 38, at 2-3 (statement of Dr. Lester Crawford) (discussing the policy goals of the Hatch-Waxman Amendment).

⁴⁰ See *Biologic Medicine Hearing, supra* note 38, at 4 (statement of Sen. Orrin Hatch). This view is heavily advocated by pioneer or innovator drug firms. See, e.g., Biotechnology Industry Organization, <http://www.bio.org>. The Biotechnology Industry Organization (BIO) is perhaps the strongest advocate on this side of the debate and comprised of more than 1,000 biotechnology companies, including major pharmaceutical manufacturers, academic institutions, and biotechnology centers. *Id.*

⁴¹ See Letter from Sara Radcliffe, *supra* note 29, at 2.

⁴² *Id.* Caroline Loew of Pharmaceutical Research and Manufacturers of America, the brand-name industry's trade group, stated, "The process is the product. The analytical characterization and therapeutic equivalence of a small molecule can be determined by assays. With biologics, it's nearly impossible. Analytical methods might not detect all immunogenicity. A change in the complex manufacturing of biologics can result in unpredictable changes in the finished product that can result in grave consequences." Herrera, *supra* note 16, at 1343.

⁴³ Herrera, *supra* note 16, at 1343-44.

innovator manufacturers, there are no analogous animal models that can be used as a basis for a predictive value in humans.⁴⁴

In the past, brand-name companies have frequently asserted potential risk to the American public as a means to block generic competition and, as a result, gained an extended monopoly on their products. Generic manufacturer Barr Pharmaceutical's attempt to market a generic form of Premarin, a drug derived from the urine of pregnant mares, exemplifies this trend.⁴⁵ Premarin, which was originally produced by brand-name company Wyeth, had been off-patent for decades and was free to copy as long as the generic manufacturer could prove chemical and therapeutic equivalence.⁴⁶ Barr produced a generic version of Premarin and conducted all of the tests required by the FDA.⁴⁷ However, the generic manufacturer never obtained FDA approval because Wyeth argued to the FDA that Wyeth itself was still trying to fully characterize Premarin, and, consequently, Barr could not possibly safely produce or market a safe generic.⁴⁸ For more than twenty years, Wyeth has blocked Barr's attempts to obtain approval of generic Premarin, asserting that Barr's tests are inadequate and that patients would be at risk if the FDA approved the drug.⁴⁹ Wyeth has even recruited several congresswomen and women's groups to support its campaign against a generic version of Premarin.⁵⁰

⁴⁴ Letter from Sara Radcliffe, *supra* note 29, at 2. As a result, many biotech companies advocate some type of clinical testing for follow-on manufacturers, which may not necessarily be the same program as the innovator's. *Id.* Even if follow-on manufacturers performed the same program, because each protein product is unique, the tests may not sufficiently demonstrate safety and efficacy. *Id.* Thus, BIO advocates utilizing product characterization, GMP controls, and relevant nonclinical and clinical studies in combination. *Id.* On the other hand, innovator manufacturer Pfizer makes the case that because of the enhanced complexity of generic biologics, nothing less than full-blown clinical trials will suffice to prove safety and efficacy. *Id.*

⁴⁵ See Herrera, *supra* note 16, at 1345.

⁴⁶ *Id.* For small molecule drugs, proving the chemical formula is equivalent is fairly simple because the chemical formula is printed on the product's label, in the literature, and in the Physicians' Desk Reference. *Id.* Typically, for therapeutic equivalence, the FDA permits abbreviated safety and efficacy data for generic compounds so that the generic producer does not have to undergo clinical trials. *Id.*

⁴⁷ *Id.*; see also Leila Abboud, *Raging Hormones: How Drug Giant Keeps A Monopoly on 60-Year-Old Pill*, THE WALL ST. J., Sep. 9, 2004, at http://www.hrt-info.com/hrtnews_090904.htm (last visited Jan. 5, 2007).

⁴⁸ Herrera, *supra* note 16, at 1345.

⁴⁹ *Id.*

⁵⁰ *Id.*

B. Generic Manufacturers' Interests⁵¹

Biogeneric advocates assert that academics and the generic industry generally believe that an abbreviated regulatory process "is clearly within the scope of current science."⁵² Thus, it is these advocates' position that a regulatory process can and should be codified as soon as possible at least for low to modestly complex biopharmaceuticals.⁵³ More complex biopharmaceuticals, on the other hand, should be approved on a case-by-case basis and, as technology advances, the pathway should be expanded to include these more complex products.⁵⁴

Generic manufacturers tend to rely on "economic science," rather than pure science, and advocate reliance on the FDA's own historic experience with biologics.⁵⁵ For example, advocates reason that the FDA has employed comparability for over a decade, and it should use this concept to determine equivalence.⁵⁶ Comparability emphasizes that "structure equals function," or, in other words, that a biopharmaceutical can be recognized as safe and effective for its intended use based on analytical and biological comparisons.⁵⁷ These comparisons would entail proving a similar structure through surrogate markers and an abbreviated set of end points, which would establish that the generic product is just as effective as the original.⁵⁸

To support this contention, biogeneric advocates cite brand-name manufacturers that have routinely used comparability in concert with the FDA for changes to their production processes, cell lines, manufacturing sites, and formulations of multiple biologics, such as recombinant proteins and monoclonal antibodies.⁵⁹ The FDA allows these changes based on comparability without clinical data to support

⁵¹ The Generic Pharmaceutical Association (GPhA) is one of the foremost advocates for implementing regulations for follow-on biologics.

⁵² Gordon Johnston, *GPhA Closing Remarks*, FDA/DIA Scientific Workshop on Follow-on Protein Pharmaceuticals, Feb. 16, 2005, at http://www.gphaonline.org/AM/Template.cfm?Section=FDA_Science&Template=/CM/HTMLDisplay.cfm&ContentID=1575 (last visited Jan. 5, 2007)

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ *Id.*

⁵⁸ Herrera, *supra* note 16, at 1344 (noting that the FDA "has accepted for ten years that the technology exists to change fermentation, purification, even the manufacturing site, and still produce an equivalent product to the original").

⁵⁹ Johnston, *supra* note 52.

safety or efficacy.⁶⁰ Thus, advocates assert that this same principle should be applied to generic biologics.⁶¹

II. THE CURRENT REGULATORY SYSTEMS AND ABBREVIATED PATHWAYS FOR DRUGS AND BIOLOGICS IN THE UNITED STATES

A. Biologics⁶² and Generic Biologics⁶³ Defined

The field of biologics is not only a rapidly expanding medical and economic market, but some advocates also predict that biological products, such as those derived from embryonic stem cells, will be able to cure diseases that remain untreatable today.⁶⁴ Biological medicines⁶⁵ are large, complex protein molecules derived from bacteria, farm animals, and other living organisms often by recombinant DNA processes.⁶⁶ These therapeutic protein molecules are more complex and expensive to discover, manufacture, and use than chemically

⁶⁰ *Id.*

⁶¹ *See id.*

⁶² The terms biological medicine, biological product, and biologics will all be used synonymously for the purposes of this discussion. Additionally, the terms brand-name, innovator, and pioneer will be used synonymously for the purposes of this discussion.

⁶³ The terms follow-on biologics, similar biologics, biosimilars, biogenerics, off-patent biologics, and generic biologics will all be used synonymously for the purposes of this discussion.

⁶⁴ *See Biologic Medicine Hearing, supra* note 38, at 1-2 (statement of Sen. Orrin Hatch).

⁶⁵ Examples of biological products include: monoclonal antibodies for in vivo use; proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), and other novel proteins; vaccines; immunomodulators (non-vaccine and non-allergenic products that inhibit or modify a pre-existing immune response); growth factors, cytokines, and monoclonal antibodies; cellular products; gene therapy products; blood, blood components, and plasma derived products. *See* CBER, Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, <http://www.fda.gov/cber/transfer/transfer.htm> (last visited Jan. 5, 2007).

⁶⁶ *Biologic Medicine Hearing, supra* note 38, at 1 (statement of Orrin Hatch); W. Wayt Gibbs, *Can Cells Be Generic?*, SCIENTIFIC AMERICAN 6, Dec. 2003, at 48. Biologics are complex because they are constructed from proteins, which are too complicated to make from scratch; the proteins require a certain type of folding that adds sugars and other chemicals to certain spots on the macromolecule. *Id.* *See also* Erika Jonietz, *Generic Biotech*, TECHNOLOGY REVIEW, Dec. 2004, at 56 (noting that because biologics rely on living cells, they have a “black-box” quality resulting in unexpected consequences from even the slightest changes, which thereby affects the drug’s efficacy or immunogenicity).

derived small molecule drugs.⁶⁷ Biological products are also more difficult to characterize because there are varying degrees of molecular complexity in different products (e.g., recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy).⁶⁸

There is no precise definition of a biologic drug because there is no consensus regarding what molecular weight or degree of heterogeneity (i.e., lack of uniform structure) should characterize a biologic.⁶⁹ Additionally, so-called “minor” changes in the manufacturing process may significantly alter parameters, such as the three-dimensional structure of the molecule, the amount of acido-basic variants, or the post-translational modifications.⁷⁰ Similarly, different manufacturing processes can lead to differing molecular weights for the same protein.⁷¹ As a result, the safety and efficacy of biological products are often directly related to the quality of monitoring during the manufacturing process,⁷² and this is why innovator companies assert that biologics should be defined by their manufacturing process and not the products themselves.⁷³

A generic drug is “identical, or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.”⁷⁴ Although chemically identical to their brand-name counterparts, generic drugs are typically sold at substantially lower prices.⁷⁵ The same principle and language is used for generic biologics in the United States.⁷⁶ A generic protein, for example, refers to a protein product with the same amino acid sequence, a similar structure, and the same intended use as the existing brand-name biological product.⁷⁷ However, because of the inherent nature of biologics, generic biologics are significantly more difficult to manufacture and identify as equivalent to the innovator product than

⁶⁷ *Biologic Medicine Hearing*, *supra* note 38, at 2 (statement of Orrin Hatch).

⁶⁸ European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), *Guideline on Similar Biological Medicinal Products*, at 4, Nov. 16, 2004, <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>.

⁶⁹ ESPICOM, *supra* note 5, at 4.

⁷⁰ EMA, *supra* note 68, at 4.

⁷¹ ESPICOM, *supra* note 5, at 4.

⁷² EMA, *supra* note 68, at 4.

⁷³ ESPICOM, *supra* note 5, at 4.

⁷⁴ CDER, *supra* note 11. See also *Biologic Medicine Hearing*, *supra* note 38, at 9 (statement of Dr. Lester Crawford).

⁷⁵ CDER, *supra* note 11. See also *Biologic Medicine Hearing*, *supra* note 38, at 9 (statement of Dr. Lester Crawford).

⁷⁶ In the EU, the term “follow-on biologics” is used in place of “generic biologics.”

⁷⁷ *Biologic Medicine Hearing*, *supra* note 38, at 9 (statement of Dr. Lester Crawford).

generic drugs.⁷⁸ This is due to biologics' large, complex protein molecules and their sensitive manufacturing process.⁷⁹

B. The Regulatory Overlap Between Drugs and Biologics

The FDA has different approval mechanisms and governing statutes for drugs and most biological products.⁸⁰ However, many biological products are classified as both biologics under the Public Health and Safety Act ("PHSA")⁸¹ and as drugs under the Federal Food, Drug, and Cosmetic Act ("FDCA")⁸² because of the FDCA's broad definition of the term "drug."⁸³ Ultimately, this overlap has resulted in the regulation of some biologics under the FDCA and others under the PHSA.

Before the FDA took control, the predecessor to the Center for Drug Evaluation and Research ("CDER") approved biologic products under section 505 of the FDCA,⁸⁴ which today uses the New Drug Application ("NDA") as its drug-approval pathway.⁸⁵ Simultaneously, the predecessor to the Center for Biologics Evaluation and Research

⁷⁸ *Id.*

⁷⁹ *Id.* It is argued that "different manufacturing processes for broadly the same product produce drugs with differing characteristics, such as molecular weight." ESPICOM, *supra* note 5, at 11. Differences in the manufacturing process can be dangerous to patients when there is a narrow therapeutic index or a relatively small difference between a safe, effective dose of a drug and a harmful one. *Id.* An example of differences between brand-name products of the same drug is the increased incidence of pure red cell aplasia (PRCA) in patients taking J&J's Exprex (EPO), but not in Amgen's EPO Epogen. *Id.*

⁸⁰ *Biologic Medicine Hearing, supra* note 38, at 6 (statement of Dr. Lester Crawford).

⁸¹ A "biological product" is defined more narrowly under the PHSA than a "drug" under the FDCA as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." PSHS Act, § 351(i), 42 U.S.C.A. § 262(i) (2003).

⁸² The FDCA defines "drug" by its intended use, as "(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." FD&C Act, § 201(g)(1), 21 U.S.C.A. § 321(g)(1) (2004).

⁸³ *See id.*

⁸⁴ Melissa R. Leuenberger-Fisher, *The Road to Follow on Biologics: Are We There Yet?* 23 BIOTECHNOLOGY L. REP. 389, 391-92 (2004).

⁸⁵ *Biologic Medicine Hearing, supra* note 38, at 8 (statement of Dr. Lester Crawford).

("CBER") licensed biologics under section 351 of the PHSA,⁸⁶ which today uses the Biologics Drug Application ("BLA") system to approve biologics.⁸⁷ In 1993, the FDA transferred all recombinant proteins and monoclonal antibodies to CBER except hormones, such as insulin and human growth hormones, which remained with CDER under the FDCA.⁸⁸ In 2003, the FDA also transferred some of CBER's therapeutic biologics to CDER.⁸⁹ However, the FDA has indicated that the BLA regulated biological products transferred to CDER, including any successor products, would continue to be approved under the PHSA.⁹⁰ Although the scope of CDER's jurisdictional control over some biologics is increasing,⁹¹ CBER has approved the majority of biologics under the PHSA.⁹² Further, it is likely that new biologics will continue to be regulated in the same way.⁹³

1. The FDCA System

New products that are regulated as drugs under section 505 of the FDCA must satisfy certain requirements for pre-market approval.⁹⁴ This process includes the submission of data from early stage clinical studies and three phases of human clinical trials pursuant to an

⁸⁶ *Id.* at 6.

⁸⁷ *Biologic Medicine Hearing*, *supra* note 38, at 8 (statement of Dr. Lester Crawford).

⁸⁸ *Id.* at 6.

⁸⁹ See 68 Fed Reg. 38067 (June 26, 2003). The therapeutic biological products transferred to CDER included monoclonal antibodies for in vivo use; proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), and other novel proteins, except those specifically assigned to CBER (e.g., vaccines and blood products). CDER, *supra* note 11. Immunomodulators (non-vaccine and non-allergenic products that inhibit or modify a pre-existing immune response) and growth factors, cytokines, and monoclonal antibodies were also transferred to CDER. *Id.*; see also CDER, *Therapeutic Biological Products*, <http://www.fda.gov/cder/biologics/default.htm> (last visited Jan. 5, 2007).

⁹⁰ FDA, *FDA Completes Final Phase of Planning for Consolidation of Certain Products from CBER to CDER*, FDA NEWS, <http://www.fda.gov/bbs/topics/NEWS/2003/NEW008800.html> (last visited Jan. 5, 2007).

⁹¹ See, e.g., *id.*; 68 Fed. Reg. 38067 (June 26, 2003).

⁹² Leuenberger-Fisher, *supra* note 84, at 392 (citing S. Usdin, *CDER's Abbreviated Route: Regulating Recombinant Proteins*, 10 *BIOCENTURY: BERNSTEIN REPORT ON BIOBUSINESS* 17, Apr 15, 2002, at A6).

⁹³ Leuenberger-Fisher, *supra* note 84, at 392.

⁹⁴ See *id.*; see generally CDER, *Investigational New Drug (IND) Application Process*, http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm (last visited Jan. 5, 2007).

investigational new drug (“IND”) application.⁹⁵ After the completion of the clinical trials, the sponsor files a NDA with the FDA, in which the drug sponsor provides the preclinical data and analysis, data and analyses from the IND clinical trials, drug information, and the manufacturing procedures used.⁹⁶ Regarding the manufacturing procedures, the FDA has established Good Manufacturing Practices (“GMPs”), which set minimum requirements for the methods, facilities, and controls used in the manufacturing, processing, and packaging of the drug.⁹⁷ The nature of chemical drugs allows the FDA to standardize GMPs because the chemical composition and purity of these drugs can generally be determined quite easily by chemical analysis.⁹⁸

For drug products the FDA has approved under the FDCA, manufacturers can apply to the FDA under section 505(j) of the FDCA for approval to sell generic versions of the brand-name product after the patent and other exclusivity periods have expired.⁹⁹ This is known as an abbreviated new drug application (“ANDA”) process.¹⁰⁰ Alternatively, section 505(b)(2) of the FDCA also provides for the approval of full NDAs if either the literature supports the finding that the drug is safe and effective or the FDA has previously made these findings.¹⁰¹ The FDA has stated that it believes there is less of a risk for biologic products regulated as drugs under section 505 of the FDCA as opposed to those regulated under the PHSA, and it would be willing to move forward with consideration of the former.¹⁰² This may be because biologics regulated under the FDCA are less molecularly complex (i.e., smaller molecules) than the products regulated under the PHSA.

⁹⁵ See Leuenberger-Fisher, *supra* note 84, at 392.

⁹⁶ *Id.*

⁹⁷ See *id.* (citing CDER, *Drug Application Regulatory Compliance*, <http://www.fda.gov/cder/regulatory/applications/compliance.htm> (last visited Jan. 5, 2007)).

⁹⁸ Leuenberger-Fisher, *supra* note 84, at 392-93. In contrast, not every biological product can be easily identified or measured. *Id.*

⁹⁹ *Biologic Medicine Hearing*, *supra* note 38, at 8 (statement of Dr. Lester Crawford).

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² See *id.*

a. **Section 505(j) of the FDCA**

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Amendments (“Hatch-Waxman”), made ANDAs available in section 505(j) of the FDCA.¹⁰³ The amendments established a shortcut in the approval process of generics for post-1962 drugs.¹⁰⁴ However, as biological products were just emerging in 1984, they were not considered during the drafting of Hatch-Waxman.¹⁰⁵ Thus, the PHSA does not fall within Hatch-Waxman.¹⁰⁶

Under Hatch-Waxman, generic companies can petition for permission to submit ANDAs for products that differ from the listed drug as the active ingredient, route of administration, dosage form, or strength if the change does not require a separate review of clinical data.¹⁰⁷ In lieu of clinical trials, the generic manufacturer must prove pharmaceutical equivalence (i.e., the same active ingredient in the same amount, same route of administration, same strength, and same dosage form) and bioequivalence to the brand drug.¹⁰⁸ The FDA uses these factors to ensure similar equivalence in terms of safety and effectiveness.¹⁰⁹ The FDA is statutorily prohibited from requiring additional investigation, clinical trials, or information other than proof of bioavailability from generic manufacturers.¹¹⁰ The ANDA is intended to provide all of the necessary information to determine that the generic is the same as the listed drug.¹¹¹ If the generic manufacturer establishes that the drug is the same as the brand-name

¹⁰³ *Id.*

¹⁰⁴ See Federal Food Drug and Cosmetic Act (FDCA), Pub. L. No. 75-717, § 505(j)(2)(C), 52 Stat. 1040, 1052 (1938) (codified as amended at 21 U.S.C. § 355(j)(2)(C)).

¹⁰⁵ Ainsworth, *supra* note 3, at 21.

¹⁰⁶ See *id.*

¹⁰⁷ See Federal Food Drug and Cosmetic Act (FDCA), Pub. L. No. 75-717, § 505(j)(2)(C), 52 Stat. 1040, 1052 (1938) (codified as amended at 21 U.S.C. § 355(j)(2)(C)). In addition, the Act’s provisions allow 180 days of marketing exclusivity to certain generic drug applicants and a 30-month stay on generic drug approvals during the litigation of any patent infringement issues. See *id.*

¹⁰⁸ David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 194 (2005).

¹⁰⁹ *Id.* at 194-95.

¹¹⁰ *Id.* at 195.

¹¹¹ *Id.*

and meets all GMPs, the generic sponsor can rely on the FDA's prior findings of safety and effectiveness without having to repeat costly animal and clinical research on ingredients or dosage forms.¹¹²

b. Section 505(b)(2) of the FDCA

The alternative way for a NDA sponsor to obtain abbreviated new drug approval is through the 505(b)(2) mechanism of the FDCA.¹¹³ Section 505(b)(2) of the FDCA was also added pursuant to the Hatch-Waxman Act in 1984.¹¹⁴ This mechanism allows a sponsor to rely either on the literature or the FDA's prior findings of safety and effectiveness to approve a drug product that either differs from an approved innovator product or requires additional human studies for approval.¹¹⁵ The FDA and the applicant can rely on the innovator's data for approval of a NDA without the innovator's permission as long as the applicant certifies that the application is not patent infringing.¹¹⁶

2. The PHSA System

Specifically designed for the regulation of biological products, the PHSA mandates specific manufacturing controls designed to monitor safety, purity, potency, and effectiveness of products that often cannot be entirely characterized.¹¹⁷ Additionally, the PHSA requires biologic manufacturers to hold an individual biologics license for each biological product under section 351.¹¹⁸

The pre-market approval process for a biological product under the PHSA is very similar to the small-molecule drug approval process under the FDCA, but the individual requirements for a biological product are stricter.¹¹⁹ The PHSA requires initial laboratory and animal testing, three separate phases of human clinical trials, and the resulting

¹¹² *Biologic Medicine Hearing*, *supra* note 38, at 7 (statement of Dr. Lester Crawford).

¹¹³ *See id.*

¹¹⁴ ESPICOM, *supra* note 5, at 27. This route was designed to cover NDAs and changes to previously approved drugs, not biologics. *Id.* "It has been used for around 80 approvals so far, with another 30 under consideration, according to the FDA." *Id.*

¹¹⁵ *Biologic Medicine Hearing*, *supra* note 38, at 8 (statement of Dr. Lester Crawford).

¹¹⁶ ESPICOM, *supra* note 5, at 27.

¹¹⁷ Leuenberger-Fisher, *supra* note 84, at 393.

¹¹⁸ *Id.* (citing 64 Fed. Reg. 56,441 (Oct. 20, 1999)).

¹¹⁹ Leuenberger-Fisher, *supra* note 84, at 393.

data submitted to CBER in a BLA. The data should demonstrate product safety, efficacy, purity, and potency and describe the manufacturing processes in order to gain BLA approval.¹²⁰

Because the resulting safety and purity of the product depends on the adherence to the processes outlined in the BLA, if any minor change is made to the product, process, controls, equipment, facilities, personnel, or labeling originally denoted in the application, the sponsor must notify the FDA and demonstrate that the change does not adversely affect the product's safety or effectiveness.¹²¹ Additionally, pre- and post-approval inspection of the manufacturing facilities is performed, and lot testing may be required.¹²² Unlike small-molecule drugs, oversight of the manufacturing process is a necessary component of biologics regulation and has been historically difficult.¹²³

There is no provision in the PHSa analogous to the FDCA's sections 505(j) or 505(b)(2) for abbreviated approval.¹²⁴ The FDA has stated that "regardless of the state of the science of protein characterization," it does not believe it currently has the authority to approve generic biologics under section 351 of the PHSa.¹²⁵ This is because it has not been possible to assess relative sameness with a high degree of certainty for protein drug products that are large, complex molecules derived from biological sources.¹²⁶

III. THE EUROPEAN UNION'S REGULATIONS ON BIOSIMILARS

When the EU passed legislation in 2003 that allowed companies to apply for permission to sell generic versions of biologics, many commentators expected the United States to follow.¹²⁷ During the July 2005 FDA Committee Hearing, FDA Commissioner Dr. Crawford acknowledged that technological progress regarding the chemistry of protein molecules, in addition to the European Medicine Evaluation Agency's work in this area, has increased the likelihood of the FDA's

¹²⁰ *Id.*

¹²¹ *Id.* (citing 21 C.F.R. § 601.12).

¹²² *Id.*

¹²³ *Id.* at 393-94.

¹²⁴ *Biologic Medicine Hearing, supra* note 38, at 8 (statement of Dr. Lester Crawford)

¹²⁵ *Id.*

¹²⁶ *Id.* at 9.

¹²⁷ *See* Langley, *supra* note 4, at A6.

approval of generic biologics.¹²⁸ In addition to its 2003 regulatory reforms that established specific provisions for biosimilars, by October 2005, the EU had both released guidelines on how to demonstrate similarity between a product and its reference product and closed the forum for comments.¹²⁹ The EMA has also issued guidance documents on most of the major products.¹³⁰ Thus, the EU is some years ahead of the United States on paper because lawmakers have established that the EMA can approve biogenerics.¹³¹ Furthermore, unlike the United States, the majority of the EU governments are supportive of controlled pharmaceutical spending and willing to use biogenerics as a way to contain costs.¹³²

A. European Medicines Agency

The EMA is the European equivalent of the FDA. It is a decentralized body of the EU that evaluates and supervises medicinal products throughout the EU.¹³³ To get marketing approval, companies submit one marketing authorization application to the EMA and an evaluation is then carried out by the Committee for Medicinal Products for Human Use (“CHMP”).¹³⁴ If CHMP concludes that the product’s quality, safety, and efficacy are sufficient, it adopts a “positive opinion” that is sent to the European Commission (“EC”), which transforms the opinion into a single market authorization valid throughout the EU.¹³⁵

¹²⁸ *House of Representatives Appropriations Comm., Agriculture, Rural Development, Food and Drug Administration and Related Agencies Subcomm. Comm. Hearing*, 110th Cong. 12 (2005) (statement of Lester Crawford, FDA Administrator). The FDA intended to release a plan for comment in the Fall of 2005 or Spring of 2006. *Id.* at 12-13. The “nature and quality of the comments” would then dictate when the regulations would be implemented. *Id.* However, the process could take as long as five years because of disagreements within the medical and scientific communities regarding whether this can be done. *Id.*

¹²⁹ ESPICOM, *supra* note 5, at 44.

¹³⁰ *Id.* at 3.

¹³¹ *Id.* at 18.

¹³² *Id.*

¹³³ European Medicines Agency, *About the EMEA--Structure*, <http://www.EMA.europa.eu/htms/aboutus/emeaoverview.htm> (last visited Jan. 5, 2007).

¹³⁴ *Id.*

¹³⁵ *Id.*

B. Approval Mechanisms and Data Requirements¹³⁶

The EU's regulatory reforms create a new approval process where the amount of data required is greater than that for small-molecule generic applications, but less than that for new drug applications.¹³⁷ The new regulations lay out the definition of biosimilars¹³⁸ and the mechanism to get them approved.¹³⁹ Data requirements are delineated in the Annex, updated by 2003/63/EC.¹⁴⁰ Although the legislation does not prohibit attempting to prove bioequivalence, this is not the preferred option.¹⁴¹

CHMP also issued a "Guideline on Similar Biologic Medicinal Products" in November 2004, which denotes how to demonstrate similarity between follow-on and innovator products, with an October

¹³⁶ The CHMP uses the term "similar biological product" instead of "generic medicinal product" because the follow-on biologic products, by definition, are not generic because there may be subtle differences among different manufacturers or compared with various reference products. EMEA, *supra* note 68, at 4.

¹³⁷ ESPICOM, *supra* note 5, at 42. See Directive 2004/27/ED, March 2004, which was published in the Official Journal of the European Union L136, 30.4.2004, available at http://dg3.eudra.org/F2/review/doc/final_publ/Dir_2004_27_20040430_EN.pdf (last visited Jan. 5, 2007) (*hereinafter* Directive 2004/27/ED).

¹³⁸ Directive 2004/27/ED defines a biosimilar as the following: "Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action. When a biological medicinal product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both." Introduction, clause 15.

¹³⁹ Directive 2004/27/ED lays out the mechanism for approval as follows: "Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided." Article 10, clause 4.

¹⁴⁰ ESPICOM, *supra* note 5, at 43. See Annex, available at http://dg3.eudra.org/F2/review/doc/2003_June/direct_comm_2003_63_en%20.pdf (last visited Jan. 5, 2007).

¹⁴¹ ESPICOM, *supra* note 5, at 43.

2005 deadline for comments.¹⁴² To facilitate this, CHMP has released product-specific guidelines that outline the best indicia for demonstrating equivalence between a product and its reference product using therapeutic equivalence rather than bioequivalence.¹⁴³

1. The Biosimilar Approach

The guidelines contain a “Biosimilar Approach” section that notes that the standard generic approach for chemically derived products, which consists of the demonstration of bioequivalence using a reference medicinal product and bioavailability studies, is not scientifically applicable to biological/biotechnology-derived products.¹⁴⁴ Biosimilar products are approvable if they use a reference innovator product that has already been granted a marketing authorization and the product’s data protection period has expired.¹⁴⁵ The biosimilar applicant must provide the typical pharmaceutical, chemical and biological data, bioequivalence and bio-availability data, and additional toxicological and other appropriate non-clinical and clinical data.¹⁴⁶ The additional data will depend on the level of complexity and diversity of the products, which will be dealt with on a case-by-case basis.¹⁴⁷

A biosimilar approach is based on comparability exercises for biologics.¹⁴⁸ Whether a product will gain approval under the biosimilar

¹⁴² *Id.* at 44; Paul Brown and Nicola Dagg, *European Union: Follow-on Biologics CHMP Issues Draft Guidelines on Similar Biological Medicinal Products*, LOVELLS, June 9, 2005, available at <http://www.mondaq.com/article.asp?articleid=32077&latestnews=1> (last visited Jan. 5, 2007). The revised versions of the guidelines should be published in the first quarter of 2006. E-mail from Denisa De Chiara of the EMA Pre-Authorisation Evaluation of Medicines for Human Use, Safety, and Efficacy of Medicines to Jessica Underwood (Nov. 14, 2005, 08:30:08 CST) (on file with author). See generally <http://www.EMEA.eu.int> (last visited Jan. 5, 2007).

¹⁴³ ESPICOM, *supra* note 5, at 44.

¹⁴⁴ EMEA, *supra* note 68, at 4.

¹⁴⁵ ESPICOM, *supra* note 5, at 3.

¹⁴⁶ *Id.* The data from the clinical trials will probably be more abbreviated than those required for a new drug application. *Id.* See generally EMEA, CHMP, *Guideline on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Active Substance–Non-Clinical and Clinical Issues*, June 2004, available at <http://www.emea.europa.eu/pdfs/human/ewp/309702en.pdf> (last visited Jan. 5, 2007) (discussing the clinical and non-clinical data required to show similarity to the original product in terms of quality, safety, and efficacy for applications where comparability is at issue).

¹⁴⁷ *Id.*

¹⁴⁸ EMEA, *supra* note 68, at 4.

approach will depend on the state of the art of the analytical procedures, the manufacturing processes employed, and the clinical and regulatory experiences to date.¹⁴⁹ Comparability exercises “are more likely to be applied to highly purified products” because they can be thoroughly characterized, such as biotechnology-derived medicinal products.¹⁵⁰ While the law does not specifically prohibit it, the biosimilar approach is more difficult to apply to biological medicinal products that are more difficult by nature to characterize.¹⁵¹ Thus, requirements to demonstrate safety and efficacy are essentially product-class specific, and if product-class specific guidance has not been defined, the “follow-on” biologic is determined on a case-by-case basis.¹⁵² The product-class specific guidelines, including changes in the manufacturing processes and the demonstration of similarities to the reference medicinal product, will regularly be revised according to changes in technology or the legal framework.¹⁵³

For example, the EU’s guidance on EPO establishes that “equivalent therapeutic efficiency” can be demonstrated in at least two preferably double-blind randomized parallel group clinical trials.¹⁵⁴ The guidance suggests people with renal anaemia would make the best study population because the condition is relatively sensitive to the effects of EPO.¹⁵⁵ After a titration phase, the comparative phase of trials should be at least twelve weeks, followed by a maintenance study of at least three months.¹⁵⁶ Therapeutic equivalence must be demonstrated for both pre-dialysis and haemodialysis patients.¹⁵⁷ The clinical trials should include at least three hundred patients with twelve months of immunogenicity data.¹⁵⁸ Additionally, the applicant must submit a pharmacovigilance plan to address immunogenicity and

¹⁴⁹ *Id.*

¹⁵⁰ *Id.*

¹⁵¹ *Id.* These include biological substances derived from biological sources and products for which little clinical and regulatory data exists, such as gene and cell therapy products. *Id.*

¹⁵² EMEA, *supra* note 68, at 6. *See also* Brown and Dagg, *supra* note 144, at 1. Class-product specific guidelines have been and are going to be made progressively available that address unique issues associated with the class-product, such as quality issues of comparability and clinical and non-clinical issues. *See* EMEA, *supra* note 68, at 4, 6.

¹⁵³ EMEA, *supra* note 68, at 6.

¹⁵⁴ ESPICOM, *supra* note 5, at 45.

¹⁵⁵ *Id.*

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

potentially adverse effects.¹⁵⁹ Approval for renal failure may allow the follow-on EPO to be approved for other application if the mode of action is the same and “appropriately justified by current scientific knowledge.”¹⁶⁰

2. Choice of Reference Product

The EU system attempts to establish an independent reference product. The biogeneric’s active substance must be molecularly and biologically similar to the reference product’s active substance.¹⁶¹ The biosimilar manufacturer would use the same reference product for all quality, safety, and efficacy studies so that the form, strength, and route of administration would be the same as the reference medicinal product.¹⁶² If there were differences, the manufacturer would have to provide non-clinical and/or clinical trials to establish the safety and efficacy of the generic, and it must be justified on a case-by-case basis.¹⁶³ For example, if a company manufactures a medicinal product containing interferon alfa-2a that it claims is biosimilar to another biological medicinal product, the reference medicinal product should be one containing interferon alfa-2a as its active substance.¹⁶⁴

IV. ANALYSIS OF THE POTENTIAL REGULATORY PATHWAYS FOR FOLLOW-ON BIOLOGICS AND RECOMMENDATIONS FOR THE UNITED STATES

There is currently no regulatory mechanism for most biosimilar products in the United States.¹⁶⁵ Middle of the road bystanders acknowledge that many, if not all, generic biologics will require at least some type of human clinical testing.¹⁶⁶ More lenient advocates suggest following commonsense rules in lieu of expensive, randomized clinical trials that would stymie the goal of making these drugs immediately available.¹⁶⁷ For example, equivalence could be determined using

¹⁵⁹ *Id.* Pharmacovigilance relies on spontaneous reports from health professionals to determine detrimental drug reactions. Letter from Sara Radcliffe, *supra* note 29, at 6.

¹⁶⁰ ESPICOM, *supra* note 5, at 45.

¹⁶¹ EMEA, *supra* note 68, at 5.

¹⁶² *Id.*

¹⁶³ *Id.*

¹⁶⁴ *Id.*

¹⁶⁵ See ESPICOM, *supra* note 5, at 25.

¹⁶⁶ *Biologic Medicine Hearing*, *supra* note 38, at 3 (statement of Sen. Orrin Hatch).

¹⁶⁷ Wainberg, *supra* note 23, at 1.

stringent chemical tests that are readily available.¹⁶⁸ Animal and tissue culture studies, biochemical studies, and short-term clinical trials demonstrating equivalence regarding the drugs' plasma levels and half-lives could be used to show efficacy and nontoxicity.¹⁶⁹

Additionally, although it is difficult to determine equivalence between different biogeneric products regarding the level of immunogenicity, full clinical trials might not be the answer.¹⁷⁰ Even large trials involving thousands of patients have only a small chance of pinpointing immunogenicity problems.¹⁷¹ Further, trials themselves have the potential to be dangerous by instilling a false sense of security in the parties involved.¹⁷² Thus, uncertainties surrounding biogenics might be more likely to be identified by extensive pharmacovigilance and post-marketing surveillance of patients taking the drug.¹⁷³ This way, potential problems could be dealt with and resolved as they arise.¹⁷⁴

Biogenics advocates¹⁷⁵ have argued that the FDA has the authority to approve generic biopharmaceutical NDAs under section 505(b)(2) of the FDCA and accept paper BLAs in support of biologic applications under section 351 of the PHSA.¹⁷⁶ Under section 351 of the PHSA, generic manufacturers would need to be given licensure if certain requirements, such as safety and efficacy studies, are met.¹⁷⁷ Alternatively, the FDA may have the authority to approve generic biologics under section 505(j) of the FDCA¹⁷⁸ when bioequivalence and sameness have been established.¹⁷⁹

¹⁶⁸ *Id.*

¹⁶⁹ *Id.*

¹⁷⁰ Immunogenicity is defined as the immune response that a drug elicits in the individual patient. ESPICOM, *supra* note 5, at 13. Immunogenicity can be significantly different for products that are deemed very similar, such as with EPO, where Eprex has been associated with pure red cell aplasia (PRCA), while other versions of EPO have not. *Id.* Slight changes in the molecular composition of the drug are responsible for these widely varying immune responses. *Id.*

¹⁷¹ ESPICOM, *supra* note 5, at 13.

¹⁷² *Id.*

¹⁷³ *See id.*

¹⁷⁴ *Id.*

¹⁷⁵ The Generic Pharmaceutical Association (GPhA) is one such advocate.

¹⁷⁶ *See* Generic Pharmaceutical Association, *Materials for January 30, 2002 Meeting with FDA*, at 18, available at http://www.fda.gov/cder/ogd/GPHA_Jan_21.htm (last visited Jan. 5, 2007).

¹⁷⁷ *Id.*

¹⁷⁸ *See generally* 21 U.S.C. § 355(j).

¹⁷⁹ Generic Pharmaceutical Association, *supra* note 179, at 34.

Two major areas of controversy exist regarding an abbreviated biogenerics pathway.¹⁸⁰ First, the level of clinical trial data that the generic applicant must provide is at issue.¹⁸¹ Brand name companies argue that generic manufacturers should provide the same level of data that was required for their innovator products, while generic manufacturers argue for less data.¹⁸² Secondly, the use of innovator data to support follow-on applications is at issue because innovator companies assert this is a Fifth Amendment takings issue.¹⁸³

A. Generally, Define Terms Narrowly

Regardless of the pathway eventually adopted, the strategy used by CHMP of defining terms and concepts narrowly will not only give the FDA's potential pathway flexibility, but also circumvent ambiguity. CHMP's guidelines evidence a strong effort to define each term narrowly, which redefines and eliminates many of the issues at hand. For example, the guidelines use the term "biosimilar" instead of "generic" to dispel even the expectation that a biosimilar will be exactly the same as its brand-name counterpart.¹⁸⁴ This technique will also promote a narrow construction of the regulations once they are adopted. Further, it goes towards safety and protecting consumer health because the regulations only include biogenerics that can be thoroughly compared to a reference product and excludes biogenerics that may be technologically obscure or otherwise controversial. The narrower the regulations are defined, the tighter the agency is able to control and regulate what it wants to target. Unlike drugs, this is necessary for generic biologics because of the heightened molecular complexity and the element of the unknown. This strategy allows lawmakers to permit generic biologics that are a reasonable risk, while blocking the approval of others.

Specifically, the term "biologics" encompasses a vast array of different types of molecules and products, and as a result, causes ambiguity and confusion.¹⁸⁵ If the term is tailored to a more narrow definition, appropriate legal standards will be easier to tailor.¹⁸⁶

¹⁸⁰ ESPICOM, *supra* note 5, at 41.

¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ *See id.*

¹⁸⁴ *See* EMEA, *supra* note 68, at 4.

¹⁸⁵ *See* Dudzinski, *supra* note 110, at 185.

¹⁸⁶ *Id.*

“Biologic biologics” or macro-heterogeneity molecules that are dependent on source materials should be separated from “biologic drugs” or non-small molecule products with significant control over the source material where equivalence can be characterized.¹⁸⁷ For “biologic biologics,” generics may not yet be technologically or legally possible.¹⁸⁸ Nonetheless, this classification scheme could provide a reservoir by which new biologics and biotechnologies could expand within the “biologic biologics” grouping without the restraint of a strict regulatory framework.¹⁸⁹ More importantly, some type of broad classification system would permit the creation of biogenerics within the “biologic drugs” grouping.¹⁹⁰ Further defining these broad classes into more specific subclasses would give the FDA even more flexibility to include and/or exclude different biologicals as needed. This type of classification system either precludes or significantly weakens the blanket statement that the creation or implementation of a regulatory system for generic biologics is not possible.¹⁹¹

However, the FDA and Congress must be cognizant that this strategy does not go too far. On one hand, defining terms and regulations too broadly may be over-inclusive and encompass products or ideas that were meant to be excluded. On the other hand, if regulations are defined too narrowly, the language can become meaningless and the policy is lost in semantics. For example, BIO objects to the word “comparability” when referring to inter-manufacturing situations regarding follow-on biologics.¹⁹² BIO reasons that because “comparability” is a term of art typically associated with “intra-manufacturer” situations, it should not be used outside this context.¹⁹³ This type of dispute has the potential to hamper

¹⁸⁷ *Id.* at 186-87. “Biologic biologics” includes the traditional biologics, such as vaccines, toxins, antitoxins, and viral and pathogen particles. *Id.* at 185. Technology and human manufacturing have little control over the production of these products because every manufacture and preparation can differ widely and no amount of purification can guarantee a uniform product. *Id.*

¹⁸⁸ *Id.* at 185.

¹⁸⁹ *Id.* Examples of these types of new biotechnologies would include gene therapies, somatic cell therapies, autologous grafts, cord blood and stem cells, and cells for cloning. *Id.*

¹⁹⁰ *Id.* at 187. Examples of “biologic drugs” include biological macromolecules such as polysaccharides, polynucleotides (DNA, RNA), and polypeptides (proteins). *Id.*

¹⁹¹ *Id.* at 192.

¹⁹² See Letter from Sara Radcliffe, *supra* note 29, at 4.

¹⁹³ *Id.* According to BIO, “‘comparability’ should be reserved for...changes in the manufacturing process for existing biotechnological/biological products. The requirements for demonstrating ‘similarity’ of protein products made by two different

the success of new regulations by diverting lawmakers' time and resources with issues that stymie the process. "Comparability," which BIO asserts should be completely stricken, unlike "generic," which the EU has entirely replaced with "follow-on" as a modifier for "biologic," can be defined completely contextually. Furthermore, the connotations of the two words are not analogous. Thus, lawmakers must be careful not to go too far when drafting regulations and defining terms narrowly in order to maintain the integrity of such regulations, as well as the policy and ideas behind them.

B. Potential Biogeneric Pathways Under the Current Law

1. Abbreviated Follow-On Pathway Under the FDCA System¹⁹⁴

a. 505(j)

Under section 505(j) of the FDCA, in lieu of clinical trials, the generic manufacturer must prove pharmaceutical equivalence and bioequivalence to the brand drug.¹⁹⁵ Because the FDCA was designed and created for chemical drugs, not biologics,¹⁹⁶ there is no legal basis or scientific way of proving bioequivalence under the ANDA process, which is a necessary precondition.¹⁹⁷ Biotech companies further argue that the traditionally abbreviated new drug application pathway for chemical drugs would be a poor fit for generic biologics because this system provides generic manufacturers with ingredient guidance, which would effectively "erode the profit motive that buttresses the very foundations of the biotech industry."¹⁹⁸

Additionally, the FDA is statutorily prohibited from requiring additional investigation, clinical trials, or information other than proof of bioavailability from generic manufacturers because an ANDA is intended to provide all the information necessary to determine that the generic is the same as the listed drug.¹⁹⁹ For this reason, some legal scholars argue that the use of an ANDA as a pathway to approve

manufacturers may be quite different from (and also more demanding than) those for demonstrating comparability." *Id.* at 5.

¹⁹⁴ See generally *supra* notes 14-26 and accompanying text.

¹⁹⁵ Dudzinski, *supra* note 110, at 194.

¹⁹⁶ See Ainsworth, *supra* note 3, at 21.

¹⁹⁷ See *id.*; ESPICOM, *supra* note 5, at 25.

¹⁹⁸ Herrera, *supra* note 16, at 1343.

¹⁹⁹ Dudzinski, *supra* note 110, at 194.

biogenerics is prohibited because the FDA is statutorily estopped from requesting any additional information about the generic.²⁰⁰ Without additional information regarding the biogeneric, the FDA would likely be unable to approve the application because additional information would inevitably be needed, such as clinical or non-clinical trials.²⁰¹

Finally, the FDA's initial interpretation of Hatch-Waxman in 1985 as suitable only when drug products are "identical" appears to foreclose the applicability of 505(j) to biologics.²⁰² Whether an ANDA would be applicable to a biogeneric also might depend on the FDA's conception of "sameness" or "identical" relative to biogenerics.²⁰³ For small molecules, Hatch-Waxman intended a strict reading of sameness (i.e., chemically identical molecules) making ANDAs only applicable where a generic could be proven to be literally identical to the pioneer drug.²⁰⁴ This strict interpretation severely limits the applicability of an ANDA to generic biologics as a potential regulatory pathway.²⁰⁵

b. 505(b)(2)

Section 505(b)(2) of the FDCA allows the FDA to approve drug products based on published literature and/or information already in approved applications.²⁰⁶ Because some biologics are defined as "drugs" subject to FDCA regulation,²⁰⁷ the FDA may have the authority to approve a 505(b)(2) NDA for a generic biologic if it is comparable to an approved brand-name.²⁰⁸ Generic companies would

²⁰⁰ *Id.* at 196.

²⁰¹ See *Biologic Medicine Hearing*, *supra* note 38, at 3 (statement of Sen. Orrin Hatch).

²⁰² Dudzinski, *supra* note 110, at 197. The FDA further stated "an abbreviated application will usually be reserved for duplicates of drug products previously approved under a full application." *Id.*

²⁰³ *Id.* See *supra* Section IV(A) for a discussion on the importance of defining terms in order to get a regulatory mechanism for biogenerics off the ground.

²⁰⁴ Dudzinski, *supra* note 110, at 197.

²⁰⁵ *Id.*

²⁰⁶ Generic Pharmaceutical Association, *supra* note 179, at 18.

²⁰⁷ Section 123(g) of the FDA Modernization Act (Pub. L. 105-115). Some early biologic products, such as insulins and human growth hormone (hGH), were regulated as drugs by CDER as opposed to biologics under CBER. ESPICOM, *supra* note 5, at 27.

²⁰⁸ Generic Pharmaceutical Association, *supra* note 179, at 18; see ESPICOM, *supra* note 5, at 27.

rely on the literature or prior FDA findings of safety and efficacy for innovator products without the innovator's permission.²⁰⁹

The FDA's *Guidance for Industry, Applications Covered by Section 505(b)(2)*²¹⁰ lists one example of a potential 505(b)(2) as "an application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug," which would technically make this section applicable to biologics.²¹¹ This pathway treats the application like a NDA, instead of an ANDA, but the applicant is allowed to use existing data, rather than the full clinical trials that a NDA requires, which is comparable to the new EU legislation.²¹² Furthermore, during the 2004 Senate Hearing, Dr. Lester Crawford, the Acting Commissioner of the FDA, was of the view that products approved under the FDCA are legally approvable under 505(b)(2) using "non-public data" from the innovator product's earlier approval.²¹³

On the other hand, innovator manufacturers assert that the FDA should not allow an abbreviated pathway because follow-on manufacturers should undertake some type of clinical testing, which may not be the same program as the innovator's.²¹⁴ Even if the follow-on manufacturer performed the same program, because each protein product is unique, the tests may not be sufficient to demonstrate safety and efficacy.²¹⁵ Thus, BIO advocates an approach that utilizes product characterization, GMP controls, and relevant nonclinical and clinical studies in combination.²¹⁶ Similarly, Pfizer makes the case that

²⁰⁹ ESPICOM, *supra* note 5, at 27.

²¹⁰ The FDA's *Guidance for Industry, Applications Covered by Section 505(b)(2)* was issued in October 1999 and lays out the purpose and application of section 505(b)(2). ESPICOM, *supra* note 5, at 27; FDA, *Guidance for Industry Applications Covered by Section 505(b)(2)*, <http://www.fda.gov/cder/guidance/2853dft.pdf> (last visited Jan. 5, 2007). Although the FDA regards the document as provisional, it is still current. ESPICOM, *supra* note 5, at 27.

²¹¹ See ESPICOM, *supra* note 5, at 27; FDA, *supra* note 216.

²¹² ESPICOM, *supra* note 5, at 27.

²¹³ ESPICOM, *supra* note 5, at 37; http://judiciary.senate.gov/testimony.cfm?id=1239&wit_id=3623.

²¹⁴ Letter from Sara Radcliffe, *supra* note 29, at 2.

²¹⁵ *Id.*

²¹⁶ *Id.* See also *BIO Citizen Petition Against 505(b)(2)*, at http://www.bio.org/healthcare/followon/BIO_CP--FINAL_DRAFT_4_22_03.pdf (last visited Jan. 5, 2007) (arguing against any type of abbreviated approach for biogenerics either as licensed biological products or approved as new drugs because

because of the enhanced complexity of generic biologics, nothing less than full-blown clinical trials should suffice to prove safety and efficacy.²¹⁷

However, generic manufacturer Sandoz filed a NDA application under 505(b)(2) for its biogeneric Omnitrope.²¹⁸ The FDA accepted the application, but deferred its decision in September 2004.²¹⁹ Sandoz announced that the agency could not reach a final decision due to scientific uncertainty and legal issues.²²⁰ As a result, at this point in time, the FDA seems unwilling to utilize the 505(b)(2) as a pathway for biologics. This may explain why some commentators believe that the approval of biologics will have to either wait for new regulations or be approved as new drugs using a NDA or BLA.²²¹

2. Abbreviated Follow-On Pathway Under Section 351 of the PHS Act

Approval under section 351 of PHS Act would be analogous to the “paper NDA” procedures for generic drugs prior to Hatch-Waxman.²²² At the Senate Hearing in June 2004, Dr. Lester Crawford, the Acting Commissioner of the FDA, noted that there was no legal basis for the FDA to approve biologics under section 351 of the PHS Act

of significant differences between chemical drugs and biologics that require each manufacturer to use original data to ensure patient safety). *But see* Letter on Behalf of the FDA, <http://www.fda.gov/cder/ogd/505b2-CPresponse.pdf> (last visited Jan. 5, 2007) (denying FDA’s BIO petition and other 505(b)(2) petitions).

²¹⁷ Herrera, *supra* note 16, at 1344. Pfizer further warns that “it is unethical to subject patients to any incremental risk when safe and efficacious protein biologics are available.” *Id.* See, e.g., Sabine Louet, *Lessons from Eprex for Biogeneric Firms*, 21 NATURE BIOTECHNOLOGY 956, 957 (2003) (predicting that because biologic erythropoietin alpha (EPO) triggered severe side effects from an immunogenic reaction, generic biologic companies attempting to manufacture EPO may need to focus more extensively on immunogenicity during clinical trials). *Cf.* Wainberg, *supra* note 23, at 2 (rejecting bioethical or immoral concerns in situations where these drugs may be otherwise unavailable).

²¹⁸ ESPICOM, *supra* note 5, at 29.

²¹⁹ ESPICOM, *supra* note 5, at 29.

²²⁰ *Id.*

²²¹ *Id.* at 29, 32. To get approval as an NDA or BLA, the generic manufacturer would need to conduct the full gamut of preclinical and clinical trials, which may be a lessened cost depending on the level of abridgement for these ‘generic’ biological products. *Id.* at 32.

²²² Generic Pharmaceutical Association, *supra* note 179, at 18; ESPICOM, *supra* note 5, at 29.

(“CBER”)²²³ because there is not currently an abbreviated pathway associated with the regulations. The FDA would have to amend its regulations from the currently used BLA process to allow approval of generic biologics based on a “paper BLA” submission.²²⁴ The FDA would also have to issue guidance regarding the necessary requirements for such a submission.²²⁵ Similar to an approval mechanism under 505(b)(2), the FDA would have to determine for a “paper BLA” whether the generic biologic is therapeutically equivalent to its brand-name counterpart.²²⁶ Thus, the concept of the FDCA’s abbreviated system would effectively be implemented into the PHS system.

C. Additional Considerations to Facilitate the Implementation and Success of a Biogeneric Mechanism

The FDA may opt to take certain steps to facilitate and expedite the creation and implementation of an abbreviated pathway for biologics. First, the FDA must identify and address the specific technical issues hindering the approval of generic biologics.²²⁷ One way to do this would be to commission studies by impartial organizations, such as the United States Pharmacopeia or the Institute of Medicine, in collaboration with interested parties to make these determinations and quantify exactly what is at issue.²²⁸ Second, the federal government should provide taxpayer funding for the development of process validation guidelines.²²⁹ These guidelines could delineate the manufacturing steps and assay parameters for generic biologic products.²³⁰

If the FDA can overcome the opposition from brand-name companies to allow generic companies to use brand-name data, there is already precedent for the demonstration of comparability from one biotech product to another.²³¹ The FDA allows innovator manufacturers to switch manufacturing sites and cell lines for biologic

²²³ See http://judiciary.senate.gov/testimony.cfm?id=1239&wit_id=3623 (last visited Jan. 5, 2007); ESPICOM, *supra* note 5, at 37.

²²⁴ ESPICOM, *supra* note 5, at 29.

²²⁵ *Id.*

²²⁶ *Id.*

²²⁷ See *Biologic Medicine Hearing*, *supra* note 38, at 3 (statement of Sen. Orrin Hatch).

²²⁸ *Id.*

²²⁹ *Id.*

²³⁰ *Id.*

²³¹ ESPICOM, *supra* note 5, at 12.

products and only demonstrate comparability between the old and new versions, instead of going through a full approval process each time.²³² However, because the FDA has approved two versions of the same biological product, this does not necessarily apply to two versions of the same biological product by different companies.²³³ This distinction is further compounded by the serious health risks that can occur from slight differences in manufacturing for products with a narrow therapeutic index.²³⁴ The brand-name company would have access to product data that the generic manufacturer presumably would not, unless the FDA made this available.²³⁵ Some advocates are encouraging the FDA to bring these generic and innovator interests together in order to remedy this solution.²³⁶

If the FDA accepts innovator companies' arguments that generic firms do not know what they are doing and, as a result, cannot be trusted to make safe and efficacious biologics, the FDA may force innovator companies to help them.²³⁷ A similar school of thought advocates that the optimal way to get generic biologics onto the market is for the generic and innovator companies to work together from the drug discovery stage on.²³⁸ This type of cooperation would distribute the burden of demonstrating comparability equally onto both generic and innovator firms.²³⁹ However, in light of the current animosity between innovator and generic companies²⁴⁰ and the polarized debate regarding biogenerics, this option may not gain the necessary support from all parties involved.

Finally, any biogenerics mechanism that is ultimately adopted for follow-on biologics should promote and maintain the same policy

²³² *Id.*

²³³ *Id.*

²³⁴ *Id.* at 11.

²³⁵ *Id.* at 12.

²³⁶ Herrera, *supra* note 16, at 1346.

²³⁷ See *id.* at 1345. See also Wainberg, *supra* note 23, at 2 (asserting that innovator companies should share the responsibility for treating HIV and license their products to generic firms that could then manufacture antiretroviral agents that would pass international muster. This collaboration would obviate the need to prove bioequivalence for these drugs, which could then be marketed in developing countries).

²³⁸ Herrera, *supra* note 16, at 1346.

²³⁹ *Id.*

²⁴⁰ When innovator company Genetech's president was asked whether he could envision a compromise to solve the generic biologics problem, he responded, "Sure, when pigs fly." *Id.* at 1345.

goals that were embodied in the Hatch-Waxman Amendment.²⁴¹ First, Congress should strive to preserve patent protection and a period of market exclusivity to protect the financial incentives of brand-name manufacturers.²⁴² This protection is also necessary for these manufacturers to recoup the money that was invested during the development of new drugs.²⁴³ To do this, the approval process could require the generic applicant to acknowledge the original patent holder, and approval should be delayed until all patent disputes are resolved and the statutory marketing exclusivity has expired.²⁴⁴

D. Weighing In

In light of the forgoing discussion, an abbreviated biogeneric pathway attached to the PHS system would be the optimal course for Congress to take. This course of action would only require an amendment to the PHS that would outline an abbreviated pathway for biologics, which would parallel exactly what the 1984 Hatch-Waxman Amendment did under the FDCA for chemical drugs. Additionally, this would require establishing the specific data requirements necessary to determine therapeutic equivalence. Once Congress decides that comparability can be used, the FDA must determine what constitutes a comparability program.²⁴⁵ Establishing an independent, standardized reference product for each generic, similar to what the EU has done, would help to facilitate these goals.

Using the EU's regulations as a model, comparability may largely depend on the state of the art of the analytical procedures, the manufacturing processes employed, and the clinical and regulatory experiences to date.²⁴⁶ The EU's use of separate regulations for class-specific products allows greater flexibility by defining the regulations and breaking down specific data requirements for specific classes individually. This method also permits the marketing of acceptable

²⁴¹ See Dudzinski, *supra* note 110, at 183.

²⁴² See *Biologic Medicine Hearing*, *supra* note 38, at 2-3 (statement of Dr. Lester Crawford).

²⁴³ See *id.*

²⁴⁴ *Id.* at 7-8.

²⁴⁵ See J.D. Green, L. Tsang, J.A. Cavagnaro. 'Generic' or 'Follow-on' Biologics" *Scientific Considerations and Safety Issues*. 3(7) EXPERT OPIN. BIOL. THER. 1019-22 (2003) (listing biochemical characterization studies, biological activity studies, toxicology studies, and clinical trials, among others, as key elements of a comparability program).

²⁴⁶ EMEA, *supra* note 68, at 4.

biosimilars, but excludes biologics that are too complex to be thoroughly evaluated for comparability.

Additionally, setting up the system in this way allows lawmakers to make rolling changes, to lax or tighten regulations, depending on the nature and structure of the class.²⁴⁷ This further contributes to the flexibility of the regulations. Finally, also similar to the EU's plan, the utilization or reservation by the FDA to consider products on a case-by-case basis gives the ultimate authority to the FDA, while enhancing safety by slowing down the regulatory process and preventing potentially dangerous products from entering the market without stymieing the entire class. These components would help to facilitate an effective biogenerics pathway in the United States.

Alternatively, section 505(j) and section 505(b)(2) of the FDCA are likely to be poor solutions to the issues at hand. First, these pathways would only be legally applicable to biologics that are currently regulated under the FDCA. Thus, for biologics under the PHSA, Congress would either exclude these drugs or work out a system for including them under the FDCA abbreviated pathway or equivalent. Congress could bypass this problem by going directly to the source, the PHSA, and make the abbreviated pathway under the PHSA applicable to FDCA-approved biologics, instead of trying to hammer out exceptions to an exception.

Second, there are too many legal and scientific issues to work around in both of these sections, which makes the clean slate of the PHSA the more appealing option. Under section 505(j), it is well-established that bioequivalence studies will be inadequate for biogenerics,²⁴⁸ which is the defining feature of the ANDA process. Furthermore, the nature of section 505(j) does not go to the inherent issues enmeshed in biogenerics because the section was drafted for small-molecule chemical products. For example, the FDA is statutorily prohibited from requesting additional information from the applicant, and the language of the amendment speaks in terms of "identical" generic and innovator drugs.²⁴⁹ Both of these concepts are antithetical to the nature and purpose of biogenerics.

Although section 505(b)(2) fares better than section 505(j), the PHSA is still the better option. However, section 505(b)(2) may be a viable pathway for biogeneric products that are regulated under the FDCA. The drawbacks of this section include the issue of whether or

²⁴⁷ See *id.* at 6.

²⁴⁸ ESPICOM, *supra* note 5, at 41.

²⁴⁹ *Id.*

not clinical trials would be necessary as part of this abbreviated pathway. If Congress decides that they are, this pathway would need to be modified for biogenerics (without affecting the small-molecule drugs already under this section) to include this requirement. In addition, innovator manufacturers are strongly opposed to supplying innovator data to support follow-on applications. However, these companies could likely be persuaded to concede the use of such data in exchange for pro-innovation concessions in the legislation.²⁵⁰ This would follow what was done with Hatch-Waxman in 1984 (i.e., the thirty month stay of approval).²⁵¹ Finally, the FDA's deferral of biogeneric Omnitrope's application under 505(b)(2) may be indicative of the agency's hesitancy to use this route because of its legal and/or scientific inapplicability to biogenerics. This again goes toward the FDA's intent to create new regulations together.

Congress and the FDA should and will likely require some type of clinical trials before allowing a generic biologic to be manufactured and marketed in the United States.²⁵² This will serve two purposes. First, it will serve as a "middle of the road" compromise between innovator and generic manufacturer interests. The FDA should not demand full-blown clinical trials, such as those required for innovator applicants, but enough to demonstrate immunogenicity, safety, and efficacy. Secondly, it will provide a sense of security to the patients and medical community.

In addition to the predictive and informational value of clinical trials, another factor should be taken into consideration when determining what level of clinical trials should be required: the additional cost that effectively discourages smaller generic companies from entering the market. In comparison to the ANDA process, getting a generic biologic to market is inherently more time-consuming and expensive than a chemical drug.²⁵³ This will deter companies with the least experience in running clinical trials from entering the sector because the level of deterrence is strongly correlated with the level of requisite clinical trials.²⁵⁴ Thus, at the onset of the creation and implementation of regulations for biogenerics in the United States, a low level of clinical trials should be required to satisfy industry

²⁵⁰ *Id.*

²⁵¹ *Id.*

²⁵² *See id.* at 14.

²⁵³ *Id.*

²⁵⁴ *Id.*

interests, protect the public, and draw generic companies into the market.

At some point, however, Congress should re-evaluate the requisite clinical trials for effectiveness to determine their predictive value relative to pharmacovigilance data, post-approval clinical, and the dampening effect on generic companies' entry into the market. After weighing these considerations, Congress can then decide whether to abandon this requirement or retain it. Additionally, Congress must be cognizant of the effect of requiring clinical trials for biogenerics on the availability of these products in international markets, particularly developing countries. If lives can be saved, Congress must evaluate whether lowering this requirement at the initial or post-implementation stage, at least in the international community, would be the right thing to do and then act accordingly.

Finally, the enormous benefit to the public may outweigh any potential negative effects of the marketing of biogenerics without further concrete evidence.²⁵⁵ Generic biologics will make these medicinal products available to consumers that may not have been able to afford them otherwise and significantly impact the health system and global economy. With proper warnings and without any hard scientific evidence to the contrary, it could be argued that the public should be given the option of having this alternative available, instead of being denied completely.

CONCLUSION

Economic pressures, such as costly medical treatment and burdens on the health care system, and the EMA's approval of Omnitrope's comparability studies will likely precipitate the introduction of generic biologics into the United States market. At the heart of the debate over biogenerics is a disagreement on science—brand-name companies argue along pure or hard science lines, while generic companies argue for “economic” or business science.²⁵⁶ However, each side utilizes public policy to buttress its position and make a more compelling argument. Generic interests advocate bringing low cost biologics to the American public and struggling developing nations, while brand-name companies push to keep the public safe from the potentially harmful and unforeseen side-effects of this unpredictable technology.

²⁵⁵ See generally Wainberg, *supra* note 23.

²⁵⁶ Johnston, *supra* note 52.

While the growth of the biogenerics industry is contingent on the implementation of an effective regulatory system, even once this system is implemented, the resulting economic repercussions will still be uncertain. Nonetheless, the United States should follow the EU's lead and utilize their guidelines as a model to create a pathway that will unlock this valuable technology. The strong public policy behind biosimilar technology should push lawmakers to find a way to allow generic manufacturers to market these products. By taking prophylactic measures from the beginning, such as defining terms narrowly and evaluating highly complex molecules on a case-by-case basis,²⁵⁷ a well-drafted biogeneric pathway can make this technology more safe and efficient for public use. However, lawmakers must be mindful of the intellectual property rights of innovator firms, which should be valued as the baseline of the pharmaceutical industry.²⁵⁸

When biogenerics are proven safe and effective, United States consumers, employers, and all governmental levels will potentially realize billions of dollars in savings on these reduced medications.²⁵⁹ Nonetheless, the smallest steps toward implementing an abbreviated system will likely instigate waves of litigation from adverse parties.²⁶⁰

²⁵⁷ See Outi Nieminen and Katrina Nordstrom, *Regulation of Biogenerics: A Survey of Viewpoints*, LABORATORY OF BIOCHEMISTRY AND MICROBIOLOGY 399 (2004) (concluding that biogenerics should be regulated on a case-by-case basis based on interviews by experts in the pharmaceutical industry); see also Green, *supra* note 248, at 1019-22 (stating that a case-by-case approach is favored because the extent of the data should be determined based on considerations related to product quality, the disease to be treated, product-specific clinical pharmacology/toxicology issues, and product-specific clinical trial design issues).

²⁵⁸ *Biologic Medicine Hearing*, *supra* note 38, at 3 (statement of Sen. Orrin Hatch).

²⁵⁹ Dudzinski, *supra* note 110, at 183.

²⁶⁰ *Id.*; see also Wayne H. Matelski, *Generic Biologics: Outline of Legal and Regulatory Issues*, PRACTISING LAW INSTITUTE (Sep. – Nov. 2003) (predicting that if the FDA were to publish new guidance or approve a biogeneric, innovator manufacturers would likely file lawsuits challenging the FDA's authority under the current statutory framework).

