

THE FUTURE OF GENERIC BIOLOGICS: SHOULD THE UNITED STATES “FOLLOW-ON” THE EUROPEAN PATHWAY?

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ABSTRACT

The United States is embarking on a biotechnology drug revolution. In the last few decades, biotech drugs have saved millions of lives, and the market for these miracle cures continues to grow at an astronomical rate. Unfortunately, as the market for biotech drugs is skyrocketing, drug prices are following suit. As Congress strives to make these new drugs more affordable, it must not ignore significant safety concerns unique to these revolutionary therapies. Congress should follow the lead of the European Union to create an accessible pathway for generic forms of biotech drugs that includes strict regulatory measures to ensure drug safety and efficacy.

INTRODUCTION

¶1 Though it might appear a product of modern science, biotechnology has been utilized by humans for thousands of years.² In 4000 B.C., humans first used “biotechnology” to ferment beer and to leaven bread through the use of yeast.³ Though our history is filled with other such creative uses of organisms to manufacture products,⁴ the term “biotechnology” was not used in print until the 1900’s.⁵ Today, biotechnology has been seamlessly integrated into our daily life, affecting everything from the foods we eat to the clothes we wear.⁶

¶2 Biotechnology plays a paramount role in the creation of new prescription drugs and vaccines. Biotechnological drugs (“biologics”) are

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² Biotechnology is defined as the use and manipulation of living organisms and their biological processes to create useful products. Oxford English Dictionary 210 (2d ed. 1989).

³ Biotechnology Industry Org., Time Line, <http://bio.org/speeches/pubs/er/timeline.asp> (last visited Jan. 12, 2008).

⁴ *See id.*

⁵ *See id.*

⁶ National Health Museum, Tools for Genetic Ingenuity: How Can You Remember These Uses of Biotechnology?, <http://www.accessexcellence.org/RC/AB/BA/aapost/remember.html> (last visited Jan. 12, 2008).

unique because they can replace or enhance natural proteins produced by the body.⁷ To date, the biotech drug industry has created more than 400 biotech drugs and vaccines, which help treat more than 200 diseases.⁸ These drugs and vaccines target life-threatening diseases such as cancers, HIV/AIDS, hepatitis C, and autoimmune disorders,⁹ as well as heart disease and stroke.¹⁰ Because of their ability to boost our body's ability to cope with disease, biologics have already helped more than 325 million sick people.¹¹

¶3 While the future of biotech drugs holds much promise, two factors may hamper their future development: unique safety concerns and cost. First, biologics present unique safety concerns not faced by "traditional" small-molecule chemical drugs. The most serious safety concern, unique to biologics, is "immunogenicity."¹² Immunogenicity is a patient's adverse antibody reaction to a drug in which the body perceives a drug to be a foreign microorganism or virus.¹³ Immunogenicity proved fatal in 2001, when several patients died of pure red cell aplasia after a form of the biotech drug erythropoietin caused a severe antibody reaction.¹⁴ The patients became allergic to all forms of erythropoietin, including the form found in their own bodies, and died when their bodies could not make red blood cells.¹⁵

¶4 The second factor which may hamper the future development of biotech drugs is their skyrocketing cost. From 1998 to 2006, the average cost of biologics has gone up 505 percent.¹⁶ And today, the cost of these drugs is astronomical. For example, the biotech drug Avastin—a treatment

⁷ Michal Nowicki, *Basic Facts About Biosimilars*, 30 KIDNEY BLOOD PRESSURE RES. 267, 267 (2007).

⁸ Zach Patton, *Complex Rx*, GOVERNING MAG., Oct. 2007, at 58.

⁹ Cyril T. Zaneski, "Miracle" Biotech Drugs Growing in Use and Cost, BALT. SUN, Mar. 16, 2004, at 1A.

¹⁰ PHARMACEUTICAL RES. & MFR. OF AMER., 418 BIOTECHNOLOGY MEDICINES IN TESTING PROMISE TO BOLSTER THE ARSENAL AGAINST DISEASE 1 (2006), available at <http://www.phrma.org/files/Biotech%202006.pdf>.

¹¹ Kenneth B. Seamon, Lecture at the University of Cambridge: Biotechnology Medicinal Products: Opportunities and Challenges, slide 6 (Oct. 2, 2007), available at http://www.ifpma.org/pdf/2007_10_02_Geneva_Bio_Forum_KSeamon.pdf.

¹² See Bryan A. Liang, *Endangering the Public Health*, DRUG DISCOVERY & DEV. 56, 56 (April 2007) [hereinafter Liang, *Public Health*].

¹³ Bryan A. Liang, *Regulating Follow-On Biologics*, 44 HARV. J. ON LEGIS. 363, 375 (2007) [hereinafter Liang, *Follow-On Biologics*].

¹⁴ Liang, *Public Health*, *supra* note 12, at 56.

¹⁵ *Id.*

¹⁶ Patton, *supra* note 8, at 58.

for breast and lung cancer—costs a patient \$100,000 per year.¹⁷ Other biotech drugs, such as Cerezyme—a treatment for a life-threatening enzyme deficiency—costs patients from \$200,000 to \$500,000 per year.¹⁸

¶5 One solution to the problem of rising drug costs could be the approval of generic biopharmaceutical drugs. Generics can produce significant reductions in cost because their development costs are often much lower.¹⁹ Currently, although a legislative framework approving generic biotech drugs does not exist, such a framework has existed for small-molecule chemical drugs for over twenty years.²⁰ For small-molecule drugs, generic versions of brand-name drugs have resulted in cheaper drugs: the savings from generic chemical drugs has been 30% to 80% off of the price of their brand-name counterparts.²¹ In the case of generic biologics, some experts predict only modest savings because there is little room to cut corners during development and production.²² Other experts are more optimistic,²³ arguing that even a 10% to 20% reduction in cost would save patients billions of dollars.²⁴

¶6 Although high costs have motivated U.S. legislators to begin considering a regulatory pathway for generic biotech drugs recently, the European Union (E.U.) has already implemented a regulatory pathway for “biosimilars.” Safety concerns, unveiled by the tragic incidence of pure red cell aplasia in 2001,²⁵ caused the E.U. to set up a “rigorous regulatory system,” which requires mandatory clinical testing and periodic review after a biosimilar is released.²⁶

¶7 In the U.S., safety concerns have led to a debate over whether clinical trials should be mandated by statute or whether the regulatory

¹⁷ Alex Berenson, *A Cancer Drug Shows Promise, at a Price That Many Can't Pay*, N.Y. TIMES, Feb. 15, 2006, at A1.

¹⁸ Kathleen Jaeger, *Creating a Workable Biogenerics Pathway for Patients*, 5 J. GENERIC MEDS. 1, 1 (2007), available at <http://www.palgrave-journals.com/jgm/journal/v5/n1/full/4950094a.html>.

¹⁹ Huub Schellekens, *How Similar Do 'Biosimilars' Need to Be?*, 22 NATURE BIOTECHNOLOGY, 1357, 1358 (2004) [hereinafter Schellekens, *How Similar*].

²⁰ See generally Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.

²¹ Generic Pharmaceutical Association, *Generics: Lower Cost*, <http://www.gphaonline.org/AM/Template.cfm?Section=FAQs&Template=/CM/HTMLDisplay.cfm&ContentID=2497> (last visited Apr. 2, 2008).

²² Patton, *supra* note 8, at 58.

²³ Some experts predict savings from \$50 billion to \$71 billion over a 10 year period. See *id.*

²⁴ Generic Pharmaceutical Association, *supra* note 21.

²⁵ For a brief discussion of this incident, see *supra* text accompanying notes 14–15.

²⁶ Liang, *Public Health*, *supra* note 12, at 56.

process should be left up to the Food and Drug Administration (“FDA”). Innovator companies are strong proponents of mandatory clinical trials, while generic drug manufacturers believe in a more fluid regulatory regime.²⁷ Stranded in the middle of this heated controversy are U.S. legislators. This article argues that Congress should follow the E.U.’s lead to set up a strict regulatory system for generic biologics, due to unique safety concerns inherent in their production. Congress should mandate human clinical tests and pharmacovigilance for every generic biologic until we better understand these drugs and their effects on the body.

I. THE BIOPHARMACEUTICAL DRUG REVOLUTION

¶8 In the last ten years, the sale of biologics has skyrocketed. In 2000, biologics sales accounted for only eleven percent of total drug sales in the U.S.²⁸ Five years later, this number rose to eighteen percent.²⁹ And by 2010, it is estimated that this number will increase to twenty-six percent.³⁰

¶9 Biologics are drugs or vaccines, created from the manipulation of a living organism.³¹ This manipulation often relies on biotechnology to attain a genetic sequence that will produce a desired therapy or prophylactic.³² Scientists use tools such as gene splicing³³ to manipulate the genetic code of living organisms—like plant and animal cells, viruses, bacteria, and yeasts.³⁴ Because the production of these new drugs depends on modern technology, biologics have not been on the market for long. For example, the most widely used biologic, recombinant human insulin, was not approved by the FDA until 1982.³⁵

¶10 Their fairly recent introduction into the drug market is only one of the many factors that distinguish biologics from the traditional small-molecule chemical drugs. For example, most chemical drugs are housed in capsules and delivered to patients orally in pill form.³⁶ Alternatively,

²⁷ See Huub Schellekens, *Biosimilar Therapeutic Agent: Issues with Bioequivalence and Immunogenicity*, 34 EUROPEAN J. OF CLINICAL INVESTIGATION 797, 798 (2004).

²⁸ Patton, *supra* note 8, at 58.

²⁹ *Id.*

³⁰ *Id.*

³¹ Biotechnology Industry Organization, Glossary, http://bio.org/speeches/pubs/er/glossary_b.asp (last visited Apr. 2, 2008).

³² See Lisa J. Raines, *Bad Medicine: Why the Generic Drug Regulatory Paradigm Is Inapplicable to Biotechnology Products*, J. BIOLAW & BUS., Autumn 2002, at 1, 8.

³³ PHARMACEUTICAL RES. AND MFR. OF AMER., *supra* note 10, at 1.

³⁴ Nowicki, *supra* note 7, at 267.

³⁵ Patton, *supra* note 8, at 58.

³⁶ Liang, *Follow-On Biologics*, *supra* note 13, at 366.

biologics, which are composed of enzymes, must be inhaled or injected because they are susceptible to deterioration in the stomach and intestines.³⁷ A susceptibility to deterioration also requires biopharmaceutical companies to follow strict manufacturing and storage guidelines.³⁸

¶11 A biologic's unique sensitivity to its environment can be attributed to (1) its complex structure, (2) its mode of action, and (3) the manner in which it is manufactured.³⁹ First, biologics are much more complex than chemical drugs. A biologic originates in a living organism and is composed of various proteins with varying gene sequences.⁴⁰ These proteins often show a considerable amount of non-uniformity.⁴¹ Consequently, although the structure of a chemical drug is well-defined,⁴² a biologic's complex composition makes it difficult to characterize.⁴³ These differences in composition result in a biologic's "fragile 3-dimensional structure," and a chemical drug's "well-characterized 1-dimensional structure."⁴⁴ In addition, a biologic's unique complexity is also evident in its large size. An average biologic drug molecule is 100 to 1,000 times larger than a chemical drug molecule.⁴⁵ A comparison of their relative sizes demonstrates this difference: an aspirin molecule (small-molecule drug) weighs 180 Da, while an interferon- β (biologic) weighs 19,000 Da.⁴⁶

¶12 Second, in addition to its complex structure and size,⁴⁷ a biologic's unique sensitivity to its environment can be attributed to its mode of action,

³⁷ Nowicki, *supra* note 7, at 268.

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ *Id.* A Dalton (Da) is a unit of mass used to express atomic and molecular mass. It is one twelfth of the mass of a carbon-12 (¹²C) atom at rest and in its ground state, which is approximately the mass of a hydrogen atom.

⁴¹ Schellekens, *How Similar*, *supra* note 19, at 1357.

⁴² *Id.*

⁴³ See Christopher Webster et al., *Can There Be Abbreviated Applications, Generics, or Follow-On Products?*, BIOPHARM INT'L, Jul. 2003, at 28, 34–35..

⁴⁴ Nowicki, *supra* note 7, at 268 (citing M. Karpusas, A. Whitty, L. Runkel & P. Hochman, *The Structure of Human Interferon-Beta: Implications for Activity*, 54 CELLULAR & MOLECULAR LIFE SCI. 1203 (1998)).

⁴⁵ Nowicki, *supra* note 7, at 268.

⁴⁶ *Id.*

⁴⁷ It is important to note that biologics differ in structure, size, and complexity not only from chemical drugs but also from each other. Insulin and human growth hormone, for example, are much simpler than more complex biologics. See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing of the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 110th Cong. (2007) [hereinafter *Hearing of the Subcomm. on Health*]. Their simpler structure makes these biologics more accessible to researchers than their more complex counterparts. See *id.*

which is much more complex than that of a chemical drug. In general, a biologic can affect up to one-hundred physiological processes⁴⁸ while a chemical drug will only affect a handful of processes in the body.⁴⁹ In addition, a biologic's structural complexity and complex mode of action make its effect on the human body hard to predict.⁵⁰

¶13 Third, a biologic's sensitivity to its environment can be attributed to the manner in which it is manufactured. In general, due to its complexity and unique origins, a biologic is difficult and expensive to manufacture.⁵¹ While a chemical process creates a chemical drug, the manufacture of a biotech drug requires the manipulation of genetic material and a biological process.⁵² Inherently more variable, this manipulation results each time in a unique product.⁵³

¶14 Due to the complexity and variability in the manufacture of biologics, a controlled environment and stringent safety review and testing are critical. During manufacturing, an average small-molecule drug may require 40–50 tests, while an average biologic requires up to 250 tests or more.⁵⁴ Consequently, an average biologic might require up to five times the number of safety tests required for a small-molecule drug.

¶15 Lastly, the complexity of biologics makes their manufacture much more expensive than the manufacture of chemical drugs.⁵⁵ High manufacturing costs are a substantial reason for the skyrocketing cost of biologics⁵⁶ as compared to small-molecule drugs. In the treatment of arthritis, for example, the most expensive small-molecule drug treatment costs \$300 per patient per year, while Enbrel, a biologic arthritis treatment, can cost an average of \$20,000 per patient per year.⁵⁷

⁴⁸ *Id.* (“[R]ecombinant interferon, interacts with nearly 100 genes which makes its exact mode of action really difficult to predict and explore.”).

⁴⁹ Nowicki, *supra* note 7, at 267.

⁵⁰ *See id.* (“While chemical agents usually affect one or a few processes in the living organism, the biotechnological molecule . . . interacts with nearly 100 genes which makes its exact mode of action really difficult to predict and explore.”).

⁵¹ *Id.* at 268.

⁵² Henry Grabowski, Iain Cockburn & Genia Long, *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFFAIRS 1291, 1292 (2006).

⁵³ *See Schellekens, How Similar, supra* note 19, at 1357.

⁵⁴ Webster, *supra* note 43, § 16.

⁵⁵ Patton, *supra* note 8, at 58.

⁵⁶ BEN ROBERTS, SHOULD THE F.D.A. CREATE AN EXPEDITED APPROVAL PROCESS FOR GENERIC BIOLOGIC DRUGS? 5 (2007).

⁵⁷ Patton, *supra* note 8, at 58.

II. FOLLOW-ON BIOLOGICS MAY HELP CURB COSTS

¶16 Follow-on biologics, the biotech equivalent of “generic” chemical drugs, are developed after an original biologic has lost patent protection and must be approved independent of the original.⁵⁸ Follow-on biologics are also sometimes referred to as “generic biologics”⁵⁹ and are called “biosimilars” in the E.U.⁶⁰ Even though terms such as “generic” might suggest that follow-ons are exact copies of the originals, in actuality these alternate versions are far from identical.⁶¹ They are created using a different manufacturing process and are born out of different cell lines than the original biologic.⁶² Consequently, follow-on biologics are not exact replicas of original biotech drugs, but they do treat the same medical condition and utilize the same mechanism of action as the original.⁶³

¶17 Currently, follow-on biologics go through the same clinical trials and testing as original biologics in order to get FDA approval.⁶⁴ Many follow-on manufacturers do not begin this process until after the original biologic loses patent protection in order to ensure that their product does not infringe on the innovator’s patent.⁶⁵ Because receiving FDA approval can be an expensive and timely process, the lack of an abbreviated regulatory pathway for follow-on biologics extends an originator’s patent beyond its statutory time limit.⁶⁶ Due to identical manufacturing and testing costs, follow-on biologics are also not cheaper than the originals. An “abbreviated approval process” could allow follow-on companies to cut corners during the testing phase of manufacturing, thus lowering the price of biotech drugs.⁶⁷

¶18 An abbreviated approval process already exists for chemical drugs.⁶⁸ This abbreviated process has resulted in 30% to 80% savings

⁵⁸ See Webster, *supra* note 43, §3.

⁵⁹ Bruce S. Manheim, Jr., Patricia Granahan & Kenneth J. Dow, ‘*Follow-On Biologics*’: *Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFAIRS 394, 394 (2006).

⁶⁰ Nowicki, *supra* note 7, at 258.

⁶¹ See Webster, *supra* note 43, at 29.

⁶² Nowicki, *supra* note 7, at 268.

⁶³ Richard G. Frank, *Regulation of Follow-on Biologics*, 357.9 NEW ENG. J. MED. 841, 841 (2007).

⁶⁴ ROBERTS, *supra* note 56, at 11.

⁶⁵ Gregory N. Mandel, *The Generic Biologics Debate: Industry’s Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 8, 23 (2006).

⁶⁶ *Id.*

⁶⁷ ROBERTS, *supra* note 56, at 4.

⁶⁸ *Id.* at 2.

between chemical drugs and their brand-name counterparts.⁶⁹ The abbreviated approval process for small-molecule chemical drugs was created in 1984 through the Drug Price Competition and Patent Term Restoration Act (“Hatch-Waxman Act”).⁷⁰ In the case of generic chemical drugs, the Hatch-Waxman Act lowers the bar to gaining FDA approval if an applicant shows equivalency between his generic and a chemical drug already approved by the FDA.⁷¹ The statute provides that an applicant may file an Abbreviated New Drug Application (“ANDA”) for a generic version of a “drug which has been approved for safety and effectiveness” under § 505 of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”).⁷² A generic chemical drug that met a standard of “sameness” does not have to repeat human clinical tests that his predecessor had already completed to gain FDA approval.⁷³

¶19 As written, this statute did not include drugs licensed under § 351 of the Public Health Service Act (“PHS Act”).⁷⁴ Because the great majority of biologics are licensed under the PHS Act,⁷⁵ the Hatch-Waxman Act applies mostly to chemical drugs and not biologics.⁷⁶ Only congressional action can create a regulatory scheme extending the Hatch-Waxman Act to include biologics licensed under the PHS Act.⁷⁷

III. EUROPE HAS ALREADY DEVELOPED A REGULATORY SCHEME FOR FOLLOW-ON BIOLOGICS

¶20 In 2003, the E.U. passed legislation that established an abbreviated approval process for “biosimilars,” the European equivalent of follow-on biologics.⁷⁸ This legislation empowered the European equivalent of the FDA, the European Medicines Agency (“EMA”), to set guidelines for the approval of biosimilars.⁷⁹ The European legislation further stated that the final decision to approve or reject a drug did not fall on the EMA but on

⁶⁹ Generic Pharmaceutical Association, *supra* note 21.

⁷⁰ Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 28 & 35 U.S.C.).

⁷¹ ROBERTS, *supra* note 56, at 2.

⁷² See Drug Price Competition and Patent Term Restoration Act, 21 U.S.C. § 355 (2006).

⁷³ See Frank, *supra* note 63, at 841.

⁷⁴ See Public Health Service Act, 42 U.S.C. § 262 (2006).

⁷⁵ FDA, Omnitrope (somatropin [rDNA origin]): Questions and Answers, <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm> (last visited Jan. 12, 2007).

⁷⁶ ROBERTS, *supra* note 56, at 9.

⁷⁷ See Grabowski, *supra* note 52, at 1292.

⁷⁸ See *Should the U.S. Copy the Europeans?* IP LAW & BUSINESS, May 2007.

⁷⁹ ROBERTS, *supra* note 56, at 55.

the European Commission (“EC”).⁸⁰ In 2006, the EMEA guidelines took effect—mandating comparative human trials, one year of testing, and risk-management plans.⁸¹

¶21 In practice, a generic biologic manufacturer in Europe can now claim that a drug is “similar” to a biologic that has already been approved.⁸² The manufacturer must then substantiate this claim by comparing the quality, safety, and efficacy of the new drug to the biologic already on the market.⁸³ Most importantly, the manufacturer must demonstrate comparable immunogenicity,⁸⁴ which often requires preclinical and clinical data.⁸⁵ Depending on the biologic, this demonstration of equivalency may require more trial patients than the original manufacturer needed to prove the drug’s safety in the first place.⁸⁶

¶22 To date, the EC has approved two biosimilar applications and rejected one application.⁸⁷ In April 2006, the Commission approved a generic human growth hormone, Omnitrope, and a few months later a second growth hormone, Valtropin.⁸⁸ Also during the same time period, the EMEA rejected Alpheon, a hepatitis-C treatment, because it did not find the generic to be adequately “similar” to the reference product, Roferon-A.⁸⁹

¶23 Whether these new biosimilars have resulted in price savings has not yet been determined. Some groups, like the International Alliance of Patients’ Organizations (IAPO), argue that the cost savings from biosimilars

⁸⁰ Stephan Herrera, *Biogenerics Standoff*, 22 NATURE BIOTECHNOLOGY 1343, 1344 (2004).

⁸¹ See Bryan A. Liang, *Generic Safety Risks*, THE AMERICAN SPECTATOR, July 25, 2007, http://www.spectator.org/dsp_article.asp?art_id=11780 (last visited Oct. 14, 2008) [hereinafter Liang, *Safety Risks*].

⁸² Schellekens, *How Similar*, *supra* note 19, at 1357.

⁸³ *Id.*

⁸⁴ *Id.* at 1358.

⁸⁵ *Should the U.S. Copy the Europeans?*, *supra* note 78.

⁸⁶ Schellekens, *How Similar*, *supra* note 19, at 1357.

⁸⁷ Nowicki, *supra* note 7, at 267.

⁸⁸ Gary C. Messplay & Colleen Heisey, *Follow-On FDA Watch*, “*Follow on Biologics: A regulatory update*,” *Contract Pharma A regulatory update*, WORLD SERVICES GROUP, Jun. 1, 2006, <http://www.worldservicesgroup.com/publications.asp?action=article&artid=1291> (last visited Jan. 12, 2008).

⁸⁹ Kirsty Barnes, *BioPartners’ biosimilar drug knocked back in Europe*, DRUGRESEARCHER.COM, Jul. 3, 2006, <http://www.drugresearcher.com/news/ng.asp?id=68818-biopartners-emea-biosimilar-biologic-drugs-interferon> (last visited Jan. 12, 2008).

is currently unknown.⁹⁰ While others, like the European Generics Medicines Association (EGA), disagree. EGA posits that initial pricing estimates for the European-biosimilar Omnitrope suggest a 20% to 30% cost savings.⁹¹

IV. THE U.S. IS WORKING ON ITS OWN REGULATORY PATHWAY FOR FOLLOW-ON BIOLOGICS

¶24 In the U.S., generic drug manufacturers and state and local governments are lobbying for Congress to create a regulatory pathway for follow-on biologics. Generic drug manufacturers insist there is a need for an abbreviated approval process for generic biologics and argue that the European model is too “onerous.”⁹² State and local governments are also pushing for a regulatory pathway.⁹³ State Medicaid programs spend more than \$500 million per year on recombinant human insulin alone.⁹⁴ As the high cost of follow-on biologics is taking its toll on state treasuries, state governments are looking to Congress for a solution.⁹⁵

¶25 Congress is currently considering legislation that would extend the abbreviated approval pathway that exists for generic small-molecule drugs to generic biologics.⁹⁶ Both House and Senate committees have been working to draft legislation that takes into account the competing interest of their constituents as well as balancing cost and safety.⁹⁷ Though there has not been a consensus in the House,⁹⁸ the Senate Committee on Health, Education, Labor and Pensions (“HELP Committee”) has drafted a bill that would create an abbreviated regulatory pathway for generic biologics.⁹⁹ The

⁹⁰ *EU Generic Firms Respond to “Biosimilar” Criticisms*, PHARMACY TIMES, Jan. 2007, at 46, available at

http://www.pharmacytimes.com/issues/articles/2007-01_4284.asp.

⁹¹ *EU Generic Firms Respond to “Biosimilar” Criticisms*, PHARMACY TIMES, Jan. 2007, at 46, available at

http://www.pharmacytimes.com/issues/articles/2007-01_4284.asp.

⁹² *Should the U.S. Copy the Europeans?*, *supra* note 78.

⁹³ Patton, *supra* note 8, at 58 (“The National Governors Association, among other groups, has asked Congress and the FDA to establish a regulatory framework for generic biologics.”). *See generally* National Governors Association, Medicaid Reform Policy (EC-16), at 16.2.1, available at <http://www.nga.org> (follow “Policy Positions” hyperlink; then follow “EC-16” hyperlink).

⁹⁴ Patton, *supra* note 8, at 58.

⁹⁵ *See id.*

⁹⁶ *See* ROBERTS, *supra* note 56, at 2.

⁹⁷ *See id.* at 6.

⁹⁸ Drew Armstrong, *House-Passed FDA Authorization Heads for Contentious Conference*, 2007 CQ WEEKLY 2117.

⁹⁹ ROBERTS, *supra* note 56, at 13–14.

Biologics Price Competition and Innovation Act of 2007 was introduced in the Senate in June 2007.¹⁰⁰

¶26 This Bill amends § 351 of the PHS Act to create an abbreviated approval process for generic biologics.¹⁰¹ It creates a process similar to the ANDA process for generic small-molecule drugs under the Hatch-Waxman Act. The language of the Bill states that the main requirement is a demonstration of “interchangeability” between the generic and the reference drug.¹⁰² The Bill does not mandate clinical testing and pharmacovigilance for every generic biologic, but instead leaves drug application review up to the FDA on a case-by-case basis.¹⁰³

¶27 The language of the Bill suggests that the HELP Committee intends to take a more liberal approach to approval than did the E.U. Unlike the E.U., the HELP Committee proposal does not put emphasis on clinical human studies, testing, and risk-management.¹⁰⁴ By focusing on a showing of interchangeability, and not sameness, the Bill would allow for molecular differences between a reference product and its follow-on, significantly increasing the safety risks to patients.¹⁰⁵

V. IMMUNOGENICITY: A SAFETY CONCERN UNIQUE TO BIOLOGICS

¶28 The HELP Committee Bill treats generic biologics much the same as the Hatch-Waxman Act treats generic small-molecule drugs. It thus ignores the unique safety concerns presented by biotech drugs. Immunogenicity, the body’s immune system response to a drug, is a safety concern that legislators did not face when creating the ANDA pathway for generic small-molecule drugs.¹⁰⁶ In some cases, a patient’s immune system responds to proteins in biologics by releasing a large number of anti-protein antibodies.¹⁰⁷ For vaccines, an adverse antibody response to a drug is desired.¹⁰⁸ But for the majority of biologics, an antibody response will

¹⁰⁰ See Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong., 1st Sess. (2007), available at <http://thomas.loc.gov/cgi-bin/query/z?c110:S.1695>.

¹⁰¹ See *id.*

¹⁰² See *id.* at § 2(3)(b).

¹⁰³ See generally *id.*

¹⁰⁴ Liang, *Safety Risks*, *supra* note 81.

¹⁰⁵ *Id.*

¹⁰⁶ See Liang, *Public Health*, *supra* note 12, at 56. See *supra* text accompanying notes 10–13.

¹⁰⁷ Raines, *supra* note 32, at 8.

¹⁰⁸ Liang, *Public Health*, *supra* note 12, at 56.

adversely affect the efficacy of the drug and can be toxic to the body.¹⁰⁹ In some cases, such immune responses can be life-threatening.¹¹⁰

¶29 Differences in structure, composition, and complexity between small-molecule drugs and biologics make an identical regulatory approval process inconsistent and potentially dangerous. The relatively simple structure of small-molecule drugs allows generic manufacturers to create generic drugs with identical chemical compositions and modes of action.¹¹¹ Due to their “sameness” in composition, clinical tests performed on the original drug can reliably establish the safety and efficacy of the generic copy. On the other hand, the inherent structural complexity of biologics makes them virtually impossible to copy.¹¹² Because a generic biologic has a different structure and mode of action than the original, clinical tests that measure a patient’s immune response to the originator drug cannot reliably be passed on to a generic.¹¹³

¶30 The danger of an antibody reaction to a generic biologic is further complicated because our current technology cannot adequately predict immunogenicity.¹¹⁴ Immunogenicity is greatly influenced by a wide array of factors, including patient specific factors—such as genetics and general health.¹¹⁵ Additionally an antibody response to a biologic is not always apparent until more than a year of regular drug use.¹¹⁶

¶31 Without the proper technology, the only way to measure an antibody response to a drug is through clinical studies.¹¹⁷ Recently Dr. Janet Woodcock, deputy commissioner and chief medical officer for the FDA, testified to the House that with today’s limited technology, human trials are necessary to protect against adverse antibody reactions.¹¹⁸ In some cases, clinical studies for a follow-on biologic require more patients than were required for the original.¹¹⁹ For example, when studying a follow-on biologic, researchers must not only test for antibody reactions to the new drug but also test for any antibody reactions that result from switching

¹⁰⁹ Schellekens, *How Similar*, *supra* note 19, at 1358.

¹¹⁰ Nowicki, *supra* note 7, at 270; *see also* Schellekens, *How Similar*, *supra* note 19, at 1358.

¹¹¹ *See* Grabowski, *supra* note 52, at 1292; Schellekens, *How Similar*, *supra* note 19, at 1357.

¹¹² *See* ROBERTS, *supra* note 56, at 6.

¹¹³ *See* Nowicki, *supra* note 7, at 270.

¹¹⁴ Schellekens, *How Similar*, *supra* note 19, at 1358.

¹¹⁵ *Id.* at 1359.

¹¹⁶ *Id.* at 1358.

¹¹⁷ *Id.* at 1359.

¹¹⁸ *Hearing of the Subcomm. on Health*, *supra* note 47.

¹¹⁹ Schellekens, *How Similar*, *supra* note 19, at 1359.

treatments.¹²⁰ The unpredictability of protein immunogenicity and the threat of serious health consequences demonstrate the importance of human trials and pharmacovigilance for every biologic that enters the market.

¶32 In passing a regulatory pathway for follow-on biologics, Congress must consider whether to mandate clinical trials by statute for each and every generic biologic or whether to leave this decision up to the FDA on a case-by-case basis. Proponents of a more flexible standard, argue that leaving this decision in the hands of the FDA will be the most efficient because biologics vary in size and complexity and because standards will change as technology develops.¹²¹ Others argue that mandating clinical trials by statute will ensure safety at our current stage, a stage when immunogenicity is unpredictable and clinical trials are necessary even in the most common biologics.¹²²

CONCLUSION

¶33 As Congress moves forward with passing a regulatory pathway for follow-on biologics, it should follow the E.U. lead by setting up a strict regulatory system that puts the safety of the American public first. Congress should consider the potentially dangerous implications of legislation like the HELP Bill, which applies the simplistic formulation of the Hatch-Waxman Act to complex follow-on biologics. Furthermore, it should mandate clinical trials by statute for every generic biologic instead of leaving this decision up to the FDA. In the European model, the EC acts as a check on the EMEA's power to approve a biosimilar.¹²³ Considering the diagnostic limitations in today's technology, Congress should ensure that the FDA does not cut corners in approving follow-on biologics until researchers understand and can harness any adverse effects of biologics on the body.

¹²⁰ Webster, *supra* note 43, § 15.

¹²¹ *See generally* Hearing of the Subcomm. on Health, *supra* note 47.

¹²² *See id.*

¹²³ Herrera, *supra* note 80, at 1344.