

## **WORKING THE BUGS OUT OF BIOLOGICS: A LOOK AT THE ACCESS TO LIFE-SAVING MEDICINES ACT AND FOLLOW-ON BIOLOGICS**

### **ABSTRACT**

This paper discusses The Access to Life Saving Medicines Act (Waxman-Schumer Act) introduced by Senator Clinton, Senator Schumer, and Representative Waxman, and how it seeks to solve the problems of approving follow-on biologics.<sup>1</sup> Patients suffering from cancer, AIDS, and other chronic diseases are those that will be most affected by the bill, along with those states that foot the bill for prescription drug programs like Medicaid. In an effort to relieve some of this burden, the Waxman-Schumer Act seeks to amend the Public Health Services Act much in the same way that the Hatch-Waxman Act amended the Food Drug and Cosmetics Act in 1984, providing for an abbreviated process for traditional generic drugs. Not enough was known about biologics at the time to include them in the Hatch-Waxman Act, and biologics are still subject to a “de facto” patent extension due to the lag for FDA approval of generic biologic drugs.

The Waxman-Schumer Act attempts to address the complexity of biologics and proof of equivalency to a branded biologic by focusing on therapeutic effect and manufacturing similarities. The questions are whether this approval process actually saves patients and prescription drug providers money, and whether that minimal savings is worth the abbreviation of safety and efficacy of a complex compound like a biologic. This paper answers in the affirmative and addresses the world market implications of having waited so long to take action in approval of follow-on biologics as well as standards currently in place in the

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<sup>1</sup> A “follow-on” biologic is a generic version of a brand-name biological product, which is sometimes referred to as a “generic biologic” or a “biosimilar.” Isabel Teare, *Biosimilar Warfare: The Arrival of Generic Biopharmaceuticals—The Omnitrope Decision*, 1 BIOSCIENCE L. REV. 9, 9 (2005–2006), available at <http://www.lawtext.com/pdfs/sampleArticles/Biosimilars.pdf>.

industry to alleviate the burden of proving therapeutic similarity.

Part II of this paper addresses the legal framework for existing follow-on drugs as well as the prospective framework for follow-on biologics.<sup>2</sup> Part III discusses the science behind the follow-on drugs and the differences between traditional chemical drugs and biologics, as well as recommendations for ensuring safety of follow-on biologics.<sup>3</sup> Finally, Part IV addresses the economics of delayed U.S. action in providing a framework for an abbreviated approval process along with international perspectives.<sup>4</sup>

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<sup>2</sup> *See infra* Part II.

<sup>3</sup> *See infra* Part III.

<sup>4</sup> *See infra* Part IV.

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## WORKING THE BUGS OUT

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## I. INTRODUCTION

The patenting of prescription drugs in the United States is preparing for a potential shake-up. Since the Hatch-Waxman Act<sup>5</sup> was passed in 1984, the public has reaped the benefit of an expedited approval process making drugs cheaper and generic drugs available as soon as the brand-named drug went off patent. After all, this is the goal of the patent system; to grant monopolies for a limited time (twenty years from filing for a patent) on an invention for the inventor to receive a return on his or her investment and then allow the public to benefit from the disclosure of the invention.<sup>6</sup> The problem is that the current system of generic approval does not provide for our evolving drug system, one in which many of the treacherous diseases of our time, including AIDS and cancer, are treated by advanced drugs derived not from chemistry, but from biotechnology.

## II. THE LAW

*A. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act)*

The Drug Price Competition and Patent Term Restoration Act (referred to as the Hatch-Waxman Act) was passed by Congress in 1984<sup>7</sup> and amended the Federal Food, Drug, and Cosmetic Act (FDCA)<sup>8</sup> to include provisions for the speedy approval of generic drugs before the patent on the brand drug expires.<sup>9</sup> The patent system is designed to provide a twenty year monopoly to the inventor of a novel product from the time the application is submitted to the Patent Office.<sup>10</sup> This process becomes more involved when one considers drugs because there is the added hurdle of passing the safety testing and gaining approval from the Food and Drug Administration.<sup>11</sup> The situation is

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<sup>5</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

<sup>6</sup> See 35 U.S.C.A. § 154(a)(2) (2008); see also *Sony Corp. of Am. v. Universal City Studios, Inc.*, 464 U.S. 417, 431–32 (1984).

<sup>7</sup> Drug Price Competition and Patent Term Restoration Act; Mary W. Bourke & M. Edward Danberg, *Current Trends in Hatch-Waxman Patent Litigation: A System Still in Flux*, in PHARMACEUTICAL LAW 2006, ACROSS THE PRODUCT LIFE CYCLE 939, 947 (2006).

<sup>8</sup> Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 355 (2008).

<sup>9</sup> See *id.* § 355(b)(3)(D)(i).

<sup>10</sup> 35 U.S.C.A. § 154(a)(2) (2008).

<sup>11</sup> The phrase “branded drug” refers to the inventor’s original drug, which

complicated further when one considers generic drugs, which need to provide the same safety assurances as the brand-name drug, but should be available to the public as soon as the patent on the brand-name drug expires. The Hatch-Waxman Act paved the way for traditional chemical generic drugs to be available to the public at the same time that the patent for the name drug runs out by permitting a generic drug manufacturer to seek approval from the Federal Food and Drug Administration (FDA) before the patent term of the brand drug expires without infringing that patent.<sup>12</sup> This is an example of the benefit that the patent system was meant to provide the public: the public is reaping the benefit of disclosure of the patented product (and how to make it) in exchange for the drug company's time-limited monopoly on a patented drug.<sup>13</sup>

Before the Hatch-Waxman Act, the public did not experience the maximum benefit of the bargain with a pharmaceutical patent holder. The generic needed to pass through lengthy FDA approval before marketing, but could not be manufactured without infringing the patent holder's rights.<sup>14</sup> Therefore, there was a delay between the expiration of the patent and marketing of a generic; there was a "de facto" extension of the patent.<sup>15</sup>

This bargain, allowing monopoly on an invention for its disclosure to the public, is put in perspective when one considers the value of the patented pharmaceuticals. Some forty-five billion dollars worth of pharmaceutical patents were expected to expire between 2001 and 2005 alone;<sup>16</sup> this does not mean that the branded drug will not still occupy some of the market if generics were to come on board, but this is a sign of a huge opportunity for generics. Since the patent disclosed how to make

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received a patent and has what the public has come to know as the "brand name." The phrase "generic drug" refers to the drug which is produced after the patent on the original drug expires using the safety and efficacy data from the brand drug. See Brian Porter, Comment, *Stopping the Practice of Authorized Generics: Mylan's Efforts to Close the Gaping Black Hole in the Hatch-Waxman Act*, 22 J. CONTEMP. HEALTH L. & POL'Y 177, 182, n. 37 (2005) (quoting Letter from Stuart A. Williams, Chief Legal Officer, Mylan Pharmaceuticals, Inc., to Dockets Management Branch, FDA, at 2 (Feb. 17, 2004), available at <http://sec.edgar-online.com/2004/06/30/0000950152-04-005121/Section7.asp>).

<sup>12</sup> See GRAHAM DUTFIELD, *INTELLECTUAL PROPERTY RIGHTS AND THE LIFE SCIENCE INDUSTRIES, A TWENTIETH CENTURY HISTORY* 121 (Ashgate 2003).

<sup>13</sup> See *Sony Corp. of Am. v. Universal City Studios, Inc.*, 464 U.S. 417, 429 (1984).

<sup>14</sup> See Bourke, *supra* note 7, at 949.

<sup>15</sup> *Id.* at 948.

<sup>16</sup> DUTFIELD, *supra* note 12, at 109.

the drug (or should have), the public has the benefit of other manufacturers putting the generic version of the drug on the shelf at expiration, a benefit which the public was not receiving because of the “de facto” extension of the patent term.

Prior to 1984, generic producing companies would have to submit a New Drug Application (NDA) to the FDA for approval on both safety and efficacy, following the same process as the inventor of the drug.<sup>17</sup> The Hatch-Waxman Act created a remedy by allowing for a generic producer to apply to the FDA for approval prior to the expiration of the branded drug through an Abbreviated New Drug Application (ANDA), rather than a lengthy NDA.<sup>18</sup> As of the year the Hatch-Waxman Act was passed, approximately 150 pharmaceuticals were on the market that had no approved generic equivalent, despite the fact that the patent had expired.<sup>19</sup>

Furthermore, the Hatch-Waxman Act provided for the brand drug producer’s investment in the approval process.<sup>20</sup> In recognition of the expensive and arduous safety and efficacy hurdles that the branded drug companies had to jump, which now included giving that trade secret to a generic producer, the patent term was extended for the branded drug producers.<sup>21</sup> This is referred to as a “term restoration” and is afforded to the brand drug company for 180 days, as a type of consolation prize.<sup>22</sup> This provides for exclusive marketing and a promise from the FDA not to approve subsequent ANDAs within that extended period of patent protection.<sup>23</sup>

### B. The “Abbreviated” Process

When a generic company applies to the FDA through the ANDA, there are two important benefits. First, the “de facto” extension of the brand patent term is reduced while still providing incentives for brand-name drug manufacturers to

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<sup>17</sup> FED. TRADE COMM’N, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY* 3 (July 2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf> [hereinafter *GENERIC DRUG ENTRY*].

<sup>18</sup> DUTFIELD, *supra* note 12, at 121.

<sup>19</sup> *GENERIC DRUG ENTRY*, *supra* note 17, at 4.

<sup>20</sup> *Id.* at 4–5.

<sup>21</sup> *Id.* at 4.

<sup>22</sup> *Id.* at 4–5; see 21 U.S.C.A. § 355(j)(5)(B)(iv) (2008).

<sup>23</sup> § 355(j)(5)(B)(iv)(II)(aa); *GENERIC DRUG ENTRY*, *supra* note 17, at 7.

invest in innovation.<sup>24</sup> Second, the approval of generics expedites the appearance of a cheaper version of the drug on the market to benefit the public.<sup>25</sup> The ANDA requires that the generic producing company prove that the “generic drug product has the same active ingredient, route of administration, dosage form and strength, and proposed labeling as the brand-name drug.”<sup>26</sup> Furthermore, the generic producer must show bioequivalence and must satisfy other formalities pertaining to the relationship between the patented drug and the follow-on.<sup>27</sup> This legislation reduced the time to approve a generic to as short as three months.<sup>28</sup>

### C. Boxing Out Biologics

A biologic includes allergenics (commonly, patch tests), blood products (transfusion products or pharmaceuticals developed from blood), gene therapies (replacing a patient’s faulty or missing genetic material), human tissue and cellular products, vaccines, and xenotransplantation products (use of animal cells where human cells are not available).<sup>29</sup> A key difference between traditional pharmaceuticals and biologics is the dynamic and sensitive nature of biologics, which are complex, susceptible to contamination, and require observation of aseptic technique from start to finish.<sup>30</sup> While the Hatch-Waxman Act covers traditional

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<sup>24</sup> GENERIC DRUG ENTRY, *supra* note 17, at 4–5.

<sup>25</sup> *Id.* at 5.

<sup>26</sup> *Id.*

<sup>27</sup> *Id.* The applicant must certify one of the following pertaining to the patent that the generic relates to in the Orange Book:

(I) that the required patent information has not been filed; (II) that the patent has expired; (III) that the patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (IV) that the patent is invalid or will not be infringed by the generic drug for which the ANDA applicant seeks approval.

*Id.* at 5–6.

<sup>28</sup> DUTFIELD, *supra* note 12, at 121.

<sup>29</sup> FDA, Center for Biologics Evaluation and Research, Frequently Asked Questions, <http://www.fda.gov/Cber/faq.htm> (last visited Feb. 6, 2008) [hereinafter Frequently Asked Questions]. A staggering number of biologics have been approved by the FDA, with insulin being one of the first in 1982. See Answers.com, Genetic Engineering: Science of Everyday Things, <http://www.answers.com/topic/genetic-engineering-1?cat=technology> (last visited Feb. 6, 2008).

<sup>30</sup> Frequently Asked Questions, *supra* note 29. Aseptic technique is a method of working with living things whereby the chance of contamination with pathogens is limited. See Aseptic Technique, ENCYCLOPEDIA OF SURGERY, <http://www.surgeryencyclopedia.com/A-Ce/Aseptic-Technique.html> (last visited

(chemical) pharmaceuticals, biologics were left out because in 1984 little was known of biologics, making it difficult to rely on the similarity between the generic and the brand compound.<sup>31</sup> This makes it a risky venture to say that a generic biologic could be equated to its branded counterpart in the same way as a reliably reproduced traditional chemical drug.<sup>32</sup>

Biologics are subject to the same “de facto” patent term extension as described in Part II B.<sup>33</sup> Tension has grown between the generic producers’ lobbyists, the drug manufacturers’ lobbyists, and the public need to reduce the cost of healthcare as biologics become more prevalent in treatment.<sup>34</sup> For example, one of the costliest biologics to patients and insurers is insulin.<sup>35</sup> The incidence of diabetes in the United States is growing steadily and, with that, the need for therapeutic insulin climbs.<sup>36</sup> In addition to meeting the standard of bioequivalence, there are problems with the capacity to produce generic biologics, the safety of fast-tracking biologics through the FDA approval process, and the balance with the public benefit.<sup>37</sup> Currently, the cost to patients and insurers paying for biologics can be as much as \$100,000 per year.<sup>38</sup> It is

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Feb. 6, 2008).

<sup>31</sup> See Waxman, Schumer, *Clinton Unveil Generic Biologics Bill at 11th Hour*, FDA WK., Oct. 6, 2006, available at 2006 WLNR 17320274.

<sup>32</sup> See *id.*

<sup>33</sup> See discussion *supra* Part II.B.

<sup>34</sup> See *Senator Hatch Gives His Overview on Pharmaceutical Issues*, WORLD GENERIC MARKETS, Oct. 18, 2006, available at 2006 WLNR 18078528; see also John Reichard, *Picking Right Medicare Drug Plan for Cancer is Hard to Do*, Study Says, CQ HEALTHBEAT, Oct. 20, 2006, available at 2006 WLNR 18525158.

<sup>35</sup> See Stephanie Saul, *States, Bridling at Insulin’s Cost, Push for Generics*, N.Y. TIMES, Jan. 11, 2007, at A1, available at 2007 WLNR 569437.

<sup>36</sup> See *id.* Government, individuals with diabetes, and insurance companies spend a total of \$3.3 billion on insulin therapies per year, and the price of insulin is expected to drop by twenty five percent with generics entering the market. *Id.*

<sup>37</sup> See *Less Price Flexibility, More Innovation: The Market Dynamics of Targeted Therapeutics*, PHARMA MARKETLETTER, Oct. 16, 2006, available at 2006 WLNR 18074778 (discussing the benefits and various hurdles accompanying biologics); see also Val Brickates Kennedy, *Pfizer Eyes Generic Biologics Market*, MARKETWATCH, Mar. 7, 2006, available at <http://www.marketwatch.com/News/Story/Story.aspx?guid={13CC469B-AE9C-4137-8B48-E832E57896CF}&tool=1&symb=PFE&sid=3746&siteid=bigcharts&dist=bigcharts> (noting problems of capacity and lack of a definitive process relating to the approval of generic biologics).

<sup>38</sup> *Waxman-Schumer Bill Hailed by GPhA*, 28 CHAIN DRUG REV., Oct. 23, 2006, available at 2006 WLNR 19418876.

projected that, as of 2010, biologic pharmaceuticals are “to reach \$60 billion in sales.”<sup>39</sup> The need is great, as would be the public benefit from an expedited generic biologics approval system; the question now is whether the Waxman-Schumer Act can satisfy those needs and ensure public safety.

*D. The Access to Life-Saving Medicines Act of 2007 (Waxman-Schumer Act)*

In September of 2006, Representative Waxman, Senator Clinton, and Senator Schumer reintroduced The Access to Life-Saving Medicine Act (hereinafter Waxman-Schumer Act), which provides for the fast-tracking of generic biologics in response to the long-felt need for the inclusion of biologics in an abbreviated FDA approval process for generic drugs.<sup>40</sup> The Waxman-Schumer Act would amend the Public Health Services Act (PHSA), which allows follow-on biologics that share principle molecular features of the branded drug to use the safety and efficacy information of the branded drug.<sup>41</sup>

There is some doubt as to the resulting savings to patients because of the high cost of manufacturing facilities and the current lack of capacity. However, the opportunity for the generic biologics to grow would be great.<sup>42</sup> Biologic sales of \$58 billion were reported in 2005 alone, and both generic manufacturers and patients stand to reap the benefit of such a massive market.<sup>43</sup> The savings that will result from generic biologics for those purchasing the generic drugs rather than the brand-name drugs, even considering the current cost of capacity growth and investment in manufacturing facilities by generic

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<sup>39</sup> *Id.*

<sup>40</sup> Press Release, Sen. Hillary Rodham Clinton, Waxman, Schumer, Clinton Introduce “Access to Life-Saving Medicines Act” (Sept. 29, 2006), available at <http://clinton.senate.gov/news/statements/details.cfm?id=264152&&>; Access to Life-Saving Medicine Act of 2006, H.R. 6257, 109th Cong. §§ 1, 2, 3(a)(2)(k)(1) (2d Sess. 2006). The Act was reintroduced by Rep. Waxman in February of 2007. Access to Life-Saving Medicine Act of 2007, H.R. 1038, 110th Cong. (1st Sess. 2007).

<sup>41</sup> Gary Messplay, *Follow-Up With Follow-On Biologics*, WORLD SERVICES GROUP, Apr. 27, 2007, available at <http://www.worldservicesgroup.com/publications.asp?action=article&artid=1956>

<sup>42</sup> *Omnitrope’s US Appro Sets No Precedents for Biogenerics, Says Wood Mackenzie*, PHARMA MARKETLETTER, June 19, 2006, available at 2006 WLNR 10630982 [hereinafter *Omnitrope*].

<sup>43</sup> *Id.*

producers, is estimated at twenty percent.<sup>44</sup> Biologic drugs are currently the most expensive part of the nation's healthcare bill and there is no end in sight with what is essentially an indefinite monopoly for these brand-name drug manufacturers.<sup>45</sup>

In response to the need of chronically ill patients, including those living with cancer and AIDS, the Waxman-Schumer Act is meant to provide life-saving medicines, which are otherwise far outside the budget of most patients.<sup>46</sup> This outcry for generic biologics has been long-felt, however, for good reason: the science surrounding biologics is more complex and not as easily replicated, making approval of a generic more challenging.<sup>47</sup> Several requirements of a follow-on biologic are addressed in the Waxman-Schumer Act, including the nature of the compound itself, the fidelity of the method of production to the branded biologic, and the state of the manufacturing facility.<sup>48</sup> This seems to indicate evaluation on a drug-by-drug basis, with more complex drugs perhaps receiving more scrutiny than a relatively common biologic that has been on the market for years, like insulin.<sup>49</sup>

#### *E. The 505(b)(2) Route Becomes VIP<sup>50</sup> Only*

It may come as a surprise that the FDA has already approved follow-on biologics by means of an existing route: the use of section 505(b)(2) of the FDCA.<sup>51</sup> Four biotechnology drugs have already been approved through this pathway.<sup>52</sup> This seemed to provide hope for the approval of generic biologics without waiting for legislation. However, the FDA spoke out on Novartis' drug Omnitrope, the first biologic approved via the 505 (b)(2) pathway, to say that the only drugs bound for approval under 505 (b)(2) are a very limited number of "follow-on proteins" and not "generic

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<sup>44</sup> *See id.*

<sup>45</sup> Press Release, Sen. Hillary Rodham Clinton, *supra* note 40.

<sup>46</sup> *See Waxman-Schumer Bill Hailed by GPhA*, *supra* note 38.

<sup>47</sup> *See id.*

<sup>48</sup> Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. §§ 3(k)(1)(A)–(B), (F)–(G) (1st Sess. 2007).

<sup>49</sup> *See* Dawn Willow, *The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare*, 6 CHI.-KENT J. INTELL. PROP. 32, 41–42 (2006).

<sup>50</sup> Gary S. Firestein, *VIP: A Very Important Protein in Arthritis*, 7 NATURE MEDICINE 537, 537 (2001), available at [http://www.nature.com/nm/journal/v7/n5/full/nm0501\\_537.html](http://www.nature.com/nm/journal/v7/n5/full/nm0501_537.html) (noting that VIP stands for Very Important Proteins).

<sup>51</sup> 21 U.S.C.A. § 355(b)(2) (2008); *Omnitrope*, *supra* note 42.

<sup>52</sup> *Omnitrope*, *supra* note 42.

biological[s]” in general.<sup>53</sup> The FDA made it quite clear that the agency was drawing the line at those smaller molecules, “follow-on proteins,” for which the branded drug had been approved under the auspices of the Public Health Services Act (PHSA) in the 1970s.<sup>54</sup> Essentially, if your drug had been approved under PHSA, you qualified for the 505 (b)(2) pathway. This path may have provided a less structured route with analysis on a case-by-case basis, but perhaps this would have been the bolder, but safer choice initiated by the FDA to ensure similarity between the follow-on and the branded drug.

Surprisingly, another “follow-on protein” that would qualify for approval under 505(b)(2) is insulin, one of the most expensive drugs for health care providers, insurers, and patients.<sup>55</sup> The FDA worked intensively to provide guidelines for the submission of follow-on insulin compounds, yet since 2002 the FDA has held back these guidelines, preferring to wait for Congress to provide legislation for all generic biologics rather than blazing a trail for a select group of proteins through this 505 (b)(2) pathway.<sup>56</sup> Now that the Waxman-Schumer Act has been presented to Congress, the FDA will likely decline to release the guidelines and choose instead to funnel insulin compounds through the framework hoped to be established by the Waxman-Schumer Act.<sup>57</sup>

The idea that the 505 (b)(2) pathway should be used, providing a comprehensive case-by-case analysis for those drugs that qualify, does not go unopposed. In approving the drug Fortical by the 505(b)(2) pathway, where the manufacturer Unigene relied on the safety and efficacy data from the branded drug produced by Novartis, the drug was approved despite vast differences in the production methods of the two drugs.<sup>58</sup> The FDA essentially stated in a letter to a party challenging the decision that pursuing further investigation would have wasted resources and slowed the time of approval.<sup>59</sup> Other than the

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<sup>53</sup> *See id.*

<sup>54</sup> *Id.*

<sup>55</sup> *See* Saul, *supra* note 35, at A1.

<sup>56</sup> *Governors Prod FDA to Release Generic Insulin Guidance*, FDA WK., Aug. 11, 2006, available at 2006 WLNR 13905595; Hunton & Williams LLP, *Follow-On FDA Watch*, “*Follow on Biologics: A Regulatory Update*,” CONTRACT PHARMA (June 1, 2006), available at [http://www.hg.org/articles/article\\_1291.html](http://www.hg.org/articles/article_1291.html).

<sup>57</sup> *See* Saul, *supra* note 35, at A1.

<sup>58</sup> Gregory Mandel, *The Generic Biologics Debate: Industry’s Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 8, 18 (2006).

<sup>59</sup> *Id.*

FDA's recent official stance on not using the 505(b)(2) pathway for follow-on biologics in general,<sup>60</sup> using this method for follow-on approval does have another major disadvantage. The 505(b)(2) pathway does not provide an opportunity for proving interchangeability, meaning that the drugs would not be deemed interchangeable at the pharmacy counter.<sup>61</sup> This is an enormous problem, as the purpose of the interchangeability is to empower the pharmacist to substitute the cheaper interchangeable drug without a new prescription from the doctor.

The Waxman-Schumer Act seems to shine where the 505(b)(2) pathway falters. Safeguards in place in the Waxman-Schumer Act take the interchangeability issue into account by providing the means within an abbreviated biologic application to prove interchangeability with a brand drug.<sup>62</sup> The Waxman-Schumer Act also provides incentives in the form of tax breaks for clinical trials necessary to prove interchangeability.<sup>63</sup> This is one serious flaw in the 505(b) route: the lack of interchangeability at the pharmacy counter. Because the 505(b) pathway is an approval process for slight variation on the branded drug, the biologics fit the framework, but are also naturally excluded from being interchangeable. It is a "Catch-22." The reason that the product is qualified is the very reason why it cannot reach the status of interchangeability. The Waxman-Schumer Act overcomes this flaw by focusing on a comparable standard based in therapeutic effect rather than exact chemical identity.

### III. THE SCIENCE

#### A. *The Waxman-Schumer Act's Safeguards*

The Hatch-Waxman Act provides for an abbreviated process where the generic drug is proven to be "substantially the same," a phrase that carries great weight because equivalence is at the center of the debate about biologics. In fact, some doubt exists as to whether equivalence is possible at all.<sup>64</sup> Living things (or that

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<sup>60</sup> See *Omnitrope*, *supra* note 42.

<sup>61</sup> See FDA, *Omnitrope Questions and Answers*, <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm> (last visited Sept. 22, 2008).

<sup>62</sup> H.R. 1038, 110th Cong. §§ 3(k)(1)(A), 3(k)(1)(C) (1st Sess. 2007).

<sup>63</sup> See *id.* at § 3(k)(17)(A)(ii).

<sup>64</sup> See Abby Christopher, *Biogenerics and Drug Pricing: A Battle Royal*, *PHARMACY TIMES*, Dec. 2006, available at <http://www.pharmacytimes.com/Article.cfm?Menu=1&ID=4186> (discussing the

which springs from them) are inherently different and incapable of being labeled the “same.”<sup>65</sup> The Waxman-Schumer Act that has been proposed for biologics requires that the proposed generic biologic and the branded biologic be “comparable.”<sup>66</sup> This result is counterintuitive when the purpose for proving similarity is to use the safety and efficacy information from the branded drug in order to shorten the FDA approval time. Therefore, a “comparable” biologic will have “comparable” safety and efficacy information. There is skepticism about the FDA’s capacity to evaluate that “comparable” status with a more complex product than a mere chemical compound.<sup>67</sup>

A now well-publicized case in the European Union (EU) tends to affirm the stance of the big biotech producers that the slightest variation makes a different drug with a different profile and produces different reactions.<sup>68</sup> The drug Eprex<sup>69</sup> was marketed in Europe by Johnson & Johnson and there was a minor change in the manufacturing of the drug.<sup>70</sup> This resulted in patients developing a mysterious allergic reaction called pure red-cell aplasia.<sup>71</sup> Pure red-cell aplasia<sup>72</sup> requires that patients be given transfusions for the rest of their lives due to the suppression of red-cell production.<sup>73</sup> This case is a reminder of how the process

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concern that “makers of biogenerics will not be able to meet criteria for safety, efficacy, and comparability”).

<sup>65</sup> See Saul, *supra* note 35, at A1.

<sup>66</sup> H.R. 1038, §§ 2(a)(4), 3(k)(1)(B)–(C).

<sup>67</sup> See Alix Weisfeld, Comment, *How Much Intellectual Property Protection Do the Newest (and Coolest) Biotechnologies Get Internationally?*, 6 CHI. J. INT’L L. 833, 833–34, 839–40, 850 (2006).

<sup>68</sup> See Saul, *supra* note 35, at A1; see also 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, 148–49 (2005).

<sup>69</sup> *Problems at J & J Plant*, CARIBBEAN UPDATE, Sept. 1, 2002, available at 2002 WLNR 4988135 (noting that Eprex is used to boost red cell production in patients undergoing dialysis or chemotherapy).

<sup>70</sup> Saul, *supra* note 35, at A1.

<sup>71</sup> *Id.*

<sup>72</sup> Although there is no definitive explanation, pure red-cell aplasia has been described as the “formation of anti-erythropoietin anti-bodies and the subsequent halt of red blood cell production. The etiology the [sic] of anti-erythropoietin antibodies has been linked to the formation of erythropoietin aggregates, believed to be a result of a slight manufacturing change in protein stabilizer from albumin to sorbitol.” Dudzinski, *supra* note 68, at 233 (citing Sabine Louët, *Lessons from Eprex for Biogeneric Firms*, 21 NATURE BIOTECHNOLOGY 956, 956 (2003)).

<sup>73</sup> *Affymax Officials Describe Recent Developments*, BIOTECH BUS. WK., Jan. 8, 2007 at 895, available at 2007 WLNR 164382; Charles L. Bennett et al., *Pure*

of producing a biologic, unlike a traditional chemical compound, is closely interconnected to the actual end-product. The Waxman-Schumer Act may not provide enough protection in requiring comparability, but as the preceding example demonstrates, even a branded drug may have problems and still fall within the guidelines of the FDA.

The Waxman-Schumer Act provides for the submission of an “abbreviated,” “comparable,” “biological product application,” analogous to an ANDA, and requires proof of comparable methods of production, facilities, mechanism of drug action, bioequivalence, and principal molecular structure.<sup>74</sup> Some standards and guidance have been provided in the form of acceptable equivalents; these examples mainly implicate the nature of DNA replication as a source of difference from the original.<sup>75</sup> The cell’s natural machinery that replicates DNA inside the cell has high rates of error and it is practically impossible to control this infidelity within the replication cycle.<sup>76</sup> This is a common-sense scientific limitation on the “comparable” standard; the cell will not produce an identical copy of DNA during replication.<sup>77</sup> Furthermore, the Waxman-Schumer Act sets out that a viral product intended for therapy need not be identical to the brand counterpart.<sup>78</sup> This standard applies mainly to vaccines where the attenuated virus or part of a virus (which signal the immune system’s production of antibodies) need not contain the identical structure, nor could it, due to the infidelity problems mentioned above.<sup>79</sup>

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*Red-Cell Aplasia and Epoetin Therapy*, 351 NEW ENG. J. MED. 1403, 1407 (2004), available at <http://content.nejm.org/cgi/reprint/351/14/1403.pdf>.

<sup>74</sup> See H.R. 1038, 110th Cong. (1st Sess. 2007).

<sup>75</sup> *Id.* § 3(a)(k)(8)(B).

<sup>76</sup> See, e.g., Pascale David et al., *DNA Replication and Postreplication Mismatch Repair in Cell-Free Extracts from Cultured Human Neuroblastoma and Fibroblast Cells*, 17 J. NEUROSCIENCE 8711, 8711, 8716, 8719 (1997), available at <http://www.jneurosci.org/cgi/reprint/17/22/8711.pdf> (discussing the infidelity in cell replication as it applies to neuroblastoma cells particularly); Dudzinski, *supra* note 68, at 232 (explaining that a small manipulation of an amino acid in a protein molecule could lead to an unsafe generic version of a drug).

<sup>77</sup> See Miroslav Radman, *Fidelity and Infidelity*, 413 NATURE 115, 115 (2001), available at [http://www.stat.ucla.edu/~dinov/courses\\_students.dir/03/Winter/STAT13.dir/STAT13\\_notes.dir/FidelityArticleNature413.html](http://www.stat.ucla.edu/~dinov/courses_students.dir/03/Winter/STAT13.dir/STAT13_notes.dir/FidelityArticleNature413.html) (noting that “in DNA replication, about [one] nucleotide is wrong in every [ten] billion”).

<sup>78</sup> See H.R. 1038, § 3(a)(k)(1)(B).

<sup>79</sup> See *id.* § 3(a)(k)(1)(A)–(B).

These provisions recognize that the process involved with manufacturing a product using life sciences or biosciences is imperfect. There are variations and complexities that are very unlike those of traditional chemical pharmaceuticals. These guidelines, however, are minimal and there is simply no way of telling at this point how the FDA will deal with the onslaught of applications if this legislation is passed. Furthermore, as the applications roll in, the FDA will be faced with the question of whether or not to approve a generic based on safety data submitted to prove therapeutic equivalence. This is a challenge when the only sure way to determine safety and efficacy is through clinical data specific to the compound in question.<sup>80</sup>

### *B. Taking Advantage of What We Already Have*

Currently, there are many alternatives that may assist the FDA in establishing standards for comparability pursuant to the Waxman-Schumer Act, if the law is enacted.<sup>81</sup> The capability of the FDA is finite and, in order to assist the evaluators, the FDA needs to establish clear boundaries for abbreviated biologic applications. Putting aside the shortcomings of a route for an abbreviated generic biologic approval process, there are two ways in which the FDA can take advantage of established mechanisms to reduce the workload of the FDA, shorten the approval process, and provide for the safety of follow-on drugs: (1) use collaborative data amassed through cooperation with the private sector to establish guidelines for approval according to a sliding scale based on molecule complexity; and (2) require use of safety insurances that have existing framework in the area of biologics development.

### *C. Ensuring Safety of Production Through the Private Sector*

The FDA has reached out to the private sector in the last few

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<sup>80</sup> See FDA, PhRMA Scientific Comments for Docket # 2004N-0355, at 7, 9, available at <http://www.fda.gov/ohrms/dockets/dockets/04n0355/04n-0355-cr00001-01-vol5.pdf>.

<sup>81</sup> See generally H.R. 1038, § 3 (describing the issues surrounding comparability in detail). See also Press Release, Sen. Charles E. Schumer, Waxman, Schumer, and Clinton Unveil Bill to Create Clear Pathway for Generic Biologic Drugs (Feb. 14, 2007), available at <http://schumer.senate.gov/SchumerWebsite/pressroom/record.cfm?id=269733&> (noting that the bill “gives the FDA the authority to require any additional clinical information it deems necessary”).

years while gearing up for the inevitable change-over to an abbreviated approval process for generic biologics.<sup>82</sup> The private industry has provided suggestions and participated in helpful dialogue with the FDA to begin framing the issues for the approval process for follow-on biologics and the safety benchmarks that the FDA could use to approve the drugs on a case-by-case basis.<sup>83</sup> In a letter from the Generic Pharmaceutical Association to the FDA, President and CEO Kathleen Jaeger suggested that the comparative performance of a biogeneric could be evaluated through various testing approaches, such as “PK/PD, animal pharmacology-toxicology testing, immunogenicity, and targeted clinical safety and efficacy testing.”<sup>84</sup>

In February of 2005, the FDA hosted a workshop where top scientists from the FDA and the private sector joined together to consider the scientific backdrop and unique scientific challenges to the follow-on approval process for biologics.<sup>85</sup> PK/PD, animal pharmacology-toxicology testing, immunogenicity, and targeted clinical safety and efficacy testing were all presented at the workshop, along with other discussions on characterization and comparability of the follow on biologic product.<sup>86</sup> Considering each approach as applied to a case-by-case approval process, one

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<sup>82</sup> See Letter from Kathleen Jaeger, President & CEO, Generic Pharm. Ass’n, to FDA (Mar. 16, 2005), available at <http://www.fda.gov/OHRMS/DOCKETS/dockets/04n0355/04n-0355-c000015-01-vol4.pdf> [hereinafter GPhA Letter] (specifically mentioning solicitations of industry comments, public forums, and the DIA-FDA Scientific Workshop on Follow-on Protein Products); see also Sara Radcliffe, *FDA, DIA Collaborate with BIO on Scientific Workshop on Follow-on Protein Pharmaceuticals*, BIO RIPL, Mar. 31, 2005, at 1, available at <http://www.bio.org/ip/newsletter/RIPLNewsletter.Issue5.pdf>.

<sup>83</sup> See GPhA Letter, *supra* note 82.

<sup>84</sup> *Id.* at 3; Phil Taylor, *Time for FDA to Move on Biogenerics*, IN-PHARMA TECHNOLOGIST.COM, Mar. 21, 2005, <http://www.in-pharmatechnologist.com/news/ng.asp?id=58874>. “PK/PD” is an industry term that refers to pharmacokinetic and pharmacodynamic research studies. A PK/PD Approach to Antibiotic Therapy, [http://www.rxkinetics.com/antibiotic\\_pk\\_pd.html](http://www.rxkinetics.com/antibiotic_pk_pd.html) (last visited Sept. 22, 2008). Pharmacokinetics is used to describe drug concentration over time and pharmacodynamics is essentially the response compared to the concentration over time. *Id.*

<sup>85</sup> See FDA, Public Workshop: Scientific Considerations Related to Developing Follow-On Protein Products, Feb. 14–16, 2005, available at [http://www.fda.gov/cder/meeting/followon/followonpresentations2\\_2005.htm](http://www.fda.gov/cder/meeting/followon/followonpresentations2_2005.htm) [hereinafter FDA Public Workshop].

<sup>86</sup> *Id.*

can see that the scientific advances since the Hatch-Waxman era are making it possible to approve very complex biologic products.

The goal is proving pharmaceutical equivalence, which certainly depends on the complexity of the molecule. For certain molecules, proving equivalence which would normally require, for example, ten steps, would only now require five; yet, a more complex molecule may still require all ten.<sup>87</sup> The common thought among scientists is that at least toxicology screening in humans, which is long and expensive, may be avoided when testing a simple molecule.<sup>88</sup> However, for a more complex molecule, a company seeking approval for the generic may have to complete the expensive screening on humans.<sup>89</sup>

One of the suggested methods for proving therapeutic equivalence, which should be used for all molecules seeking approval, includes immunogenicity testing.<sup>90</sup> Immunogenicity testing should be conducted on any molecule seeking approval because an immune response in humans to biologic products is common, and a slight variation in production could elicit such a response, defeating the efficacy of the drug and producing adverse effects on the body.<sup>91</sup> Because many of the biological drugs use animal or recombinant animal proteins, the chance for an immunological response is high.<sup>92</sup> Another safety assurance

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<sup>87</sup> For instance, if a very complex gene therapy drug were to seek follow-on approval, this very complex drug may require more extensive safety testing than a fairly simple follow-on insulin drug that has been widely produced for years with consistent results. See FDA, Human Gene Therapy and the Role of the Food and Drug Administration, (Sept. 2000), <http://www.fda.gov/cber/infosheets/genezn.htm>.

<sup>88</sup> See Transcripts, Breakout Session C: Pharmacology-Toxicology Studies, Session 1, at 14, 31, in FDA Public Workshop, *supra* note 85, available at [http://www.fda.gov/cder/regulatory/follow\\_on/200502/200502\\_transcripts\\_0214b\\_sc1.pdf](http://www.fda.gov/cder/regulatory/follow_on/200502/200502_transcripts_0214b_sc1.pdf).

<sup>89</sup> See *id.*; see also Transcripts, Breakout Session F: Clinical Safety and Efficacy Studies, Session 2, at 9-11, in FDA Public Workshop, *supra* note 85, available at [http://www.fda.gov/cder/regulatory/follow\\_on/200502/200502\\_transcripts\\_0215b\\_sf2.pdf](http://www.fda.gov/cder/regulatory/follow_on/200502/200502_transcripts_0215b_sf2.pdf).

<sup>90</sup> Immunogenicity testing is the study of the body's immunological reaction to a particular drug in order to determine if the body will have an adverse immune response to a drug. See Robin Thorpe, Presentation, *Unwanted Immunogenicity: Implications for Follow-on Biologicals*, in FDA Public Workshop, *supra* note 85, available at <http://www.fda.gov/cder/meeting/followon/Thrope.ppt>.

<sup>91</sup> See *Id.*; see also discussion *supra* Part III. A. (discussing the adverse immunological reaction, red-cell aplasia).

<sup>92</sup> See Thorpe, *supra* note 90.

that is considered essential for biologics is the process of characterization.<sup>93</sup> During the FDA private-sector meeting, Joerg Windisch, Novartis's Global Head of Technical Development, said that comparative studies of characterization are not sufficient; they may merely reduce the need for preclinical testing and dose-ranging studies, as well as reduce the size of populations in phase III testing.<sup>94</sup> This means that the approval process is "science- and data-driven" by each molecule up for approval and not based merely on comparability.<sup>95</sup> These few required steps alone raise the bar for biologics seeking follow-on approval, and there is a hefty price tag that accompanies these safety steps. This is not the end of the problems with the complexity of biologics, though. The method of production throws another kink in the approval process.

*D. Capacity to Produce Generic Biologics and Concern about Poor Manufacturing*

There is much concern over both the lack of capacity to produce generic biologics as well as the delicate nature of the process of manufacturing biologics that could lead to contamination and inconsistent results.<sup>96</sup> At the center of this debate is the facility itself, as evinced by the provision in the Waxman-Schumer Act providing for the demonstration of a comparable facility.<sup>97</sup> Due to the high demands of biologics production, there has been an increase in demand for outsourced biologics manufacturers, overseas production, and an interest in generic biologic

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<sup>93</sup> See Joerg Windisch, Presentation, *The Value of State-of-the-Art Analytical Characterization in the Development and Evaluation of Follow-on Protein Products*, in FDA Public Workshop, *supra* note 85, available at [http://www.fda.gov/cder/meeting/followon/Windisch\\_final.ppt#360,2,Introduction\(1\)](http://www.fda.gov/cder/meeting/followon/Windisch_final.ppt#360,2,Introduction(1)).

<sup>94</sup> *Id.* The phases of clinical testing include Phase I (study with a small group of people to determine safe dosage range), Phase II (the drug is given to a larger group of people to test efficacy), Phase III (the drug is given to 1,000-3,000 people to fully test things like dosage and side effects), and Phase IV (post marketing studies). Understanding Clinical Trials, ClinicalTrials.gov, <http://clinicaltrials.gov/ct2/info/understand> (last visited Sept. 22, 2008).

<sup>95</sup> Windisch, *supra* note 93.

<sup>96</sup> Ralph G. Schroeder & Paul Papas, *Protecting the Balance of Hatch-Waxman: Understanding the Industry's New Dynamics for the 21st Century*, 56 FOOD & DRUG L. J. 19, 26 (2001).

<sup>97</sup> H.R. 1038, 110th Cong. § 3(a)(k)(1)(F) (1st Sess. 2007).

production by the large pharmaceutical companies.<sup>98</sup> Because this market is basically untapped and the production of biologics is very complex, large pharmaceutical and biotech companies that produce brand drugs and have the needed capital are expanding their capacities.<sup>99</sup>

Perhaps a more promising use of existing standards and frameworks for approval of biologics should come in the form of those that provide additional standards to ease the heavy chore of proving comparability and safety. Perhaps generic manufacturers could get a step ahead by using established routes of proving safety where legislation is not needed. This may provide short-term relief from the stall in generic approval framework by giving the generic producers a way to run safety tests legally before the branded drug comes off patent. By focusing on the standards and available methods of proving safety and efficacy, the major hurdle of biologics approval may begin to be surmounted; one must prove that the process of making the biologic is safe and that the manufacturing facility is capable of making it so.

Under 35 U.S.C. § 271(e)(1) there are certain “safe harbor” exceptions to patent infringement that may be useful to a generic biologic that is seeking FDA approval and safety measures that may be used prior to filing with the FDA.<sup>100</sup> Viral clearance testing has been recognized by federal courts as a safe harbor exception under § 271.<sup>101</sup> This process is essentially the performance of a scaled-down version of the manufacturing process whereby a virus associated with the starting product (the animal from which the starting cell line was taken) is injected into the manufacture and the group seeking approval must then “clean” the sample by filtering or inactivating the virus.<sup>102</sup> The process can be conducted for all phases of manufacturing and, at times, in the facility itself in an effort to evaluate capacity for

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<sup>98</sup> See Rick Mullin, *Strategies Shift in Contract Biologics*, 84 CHEM. & ENG'G NEWS, Feb. 13, 2006, at 58–61, available at <http://pubs.acs.org/email/cen/html/021306191350.html>.

<sup>99</sup> *Id.* For instance, Amgen and Centocor have both pursued expansion of their facilities and capacities to produce biologics. *Id.*

<sup>100</sup> 35 U.S.C. § 271(e)(1) (2008).

<sup>101</sup> *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 111 (D. Mass. 1998).

<sup>102</sup> See BioReliance, *Why Perform a Viral/TSE Clearance Study?*, [http://www.bioreliance.com/why\\_perform.html](http://www.bioreliance.com/why_perform.html) (last visited Sept. 22, 2008).

clean-up and manufacture strategy.<sup>103</sup> This process does not wipe away all concerns about contamination, but it does provide reassurance to the FDA that the generic producer has the capacity to deal with the fundamental problems of biologic handling.

There has been great opposition to this safe harbor use in the past.<sup>104</sup> Following the case that pronounced viral clearance as an acceptable use of patented material under § 271,<sup>105</sup> Amgen, the largest biotechnology company in the United States, sought changes to § 271 (e)(1) to narrow the scope of the statute through legislation to only those acts that are in preparation for an ANDA.<sup>106</sup> Of course, this would have put biologics out in the cold, not being eligible for an ANDA; but the legislation did not pass.<sup>107</sup> The implications of another landmark case, *Merck KGaA v. Integra Lifesciences I, Ltd.*, give wide latitude to generic manufacturers who seek approval through the FDA by allowing the testing of capacity and evaluation of profitability in connection with pursuing FDA follow-on approval.<sup>108</sup>

Established methods of ensuring the safety and reliability of the manufacturer, like viral clearance testing, should be considered to reduce the workload and provide more translucent governance of the follow-on approval process. By making these methods mandatory, the FDA would reduce their workload while increasing the reliability and predictability of the approval process. The initial cost may be higher, however, the public benefit may be realized faster and in a more consistent and safe manner.

Biologics product-safety testing is currently available from a number of private sector companies.<sup>109</sup> Testing can include anything from production and manufacture to final product

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<sup>103</sup> See BioReliance, Viral Clearance and TSE Clearance Studies Introduction, [http://www.bioreliance.com/tse\\_intro.html](http://www.bioreliance.com/tse_intro.html) (last visited Sept. 22, 2008).

<sup>104</sup> William S. Feiler & Paula K. Wittmayer, *The Section 271(e) "Safe Harbor"—A Proposal for Legislative Change*, 25 BIOTECHNOLOGY L. REP. 123, 123 (2006).

<sup>105</sup> *Amgen*, 3 F. Supp. 2d at 111.

<sup>106</sup> Feiler, *supra* note 104, at 126.

<sup>107</sup> *Id.*

<sup>108</sup> See *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 204–05, 207 (2005).

<sup>109</sup> See, e.g., BioReliance, Testing and Manufacturing Services Overview, [http://www.bioreliance.com/about\\_us\\_intro.html](http://www.bioreliance.com/about_us_intro.html) (last visited Sept. 22, 2008).

screening.<sup>110</sup> By using the services of the private sector that are currently available, but not required, the drug companies are ensuring a more positive response from the FDA and the FDA is less burdened by the case-by-case approval process.

#### IV. THE ECONOMY

##### A. *The Crisis in U.S. Healthcare*

Currently, biologics are among the most expensive items in the U.S. healthcare budget.<sup>111</sup> The people in this country who use insulin, along with insurers and the government, are spending \$3.3 billion on the branded drug.<sup>112</sup> The price of insulin is slated to drop twenty-five percent when generics enter the market and, with the growing incidence of diabetes in the United States, the savings will only increase.<sup>113</sup> Insulin is merely one example of how the national healthcare budget struggles to keep up with costly drugs; others include Avastin, used to treat cancer, which costs as much as \$4,000 per month, and other treatments for diseases like rheumatoid arthritis and cancer, which cost “tens of thousands of dollars a year.”<sup>114</sup> The cost of insulin to state Medicaid programs alone in 2005 was \$500 million.<sup>115</sup> The United States is struggling to meet the demands of a growing need for biologic drugs, and for drugs like insulin, where the structure and manufacture is relatively simple and the brand drug is off-patent, there is no need for the wasted money. This U.S. economic crisis also has a profound effect on the low-income segment of our population, which is often ignored and suffers at the hands of big American business.<sup>116</sup>

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<sup>110</sup> See BioReliance, Contract Manufacturing Services Introduction, [http://www.bioreliance.com/manufacturing\\_intro.html](http://www.bioreliance.com/manufacturing_intro.html) (last visited Sept. 22, 2008); see also BioReliance, Safety Testing Introduction, [http://www.bioreliance.com/biosafety\\_intro.html](http://www.bioreliance.com/biosafety_intro.html) (last visited Sept. 22, 2008).

<sup>111</sup> Press Release, Sen. Hillary Rodham Clinton, *supra* note 40.

<sup>112</sup> Saul, *supra* note 35, at A1.

<sup>113</sup> *Id.*

<sup>114</sup> *Id.*

<sup>115</sup> *Id.*

<sup>116</sup> See, e.g., Seam Park, Note, *Substantial Barriers in Illegal Immigrant Access to Publicly-Funded Health Care: Reasons and Recommendations for Change*, 18 GEO. IMMIGR. L.J. 567 (2004). Currently in the United States, immigrants who have no healthcare are not receiving the vaccinations that are necessary for young children and adults alike. *Id.* at 579–80. The United States is struggling to protect the health of the weakest portion of our population and seems to be failing in the face of the extreme costs of vaccines, thereby

Barr Pharmaceuticals (Barr) has already expressed interest in entering the insulin drug market, and the only stumbling block at this point seems to be politics.<sup>117</sup> Yet Barr is not the only company that is interested in entering the market; there are two companies from India that are poised to swoop into the market for generic biologics in Europe, and potentially in the United States, if U.S. politics can get out of its own way to regulate generic biologic drugs.<sup>118</sup>

*B. United States Falling Behind by Playing it Safe*

As a result of the FDA's failure to institute an aggressive framework for follow-on biologics and the subsequent lag in competitive U.S. scale-up of biologic manufacturing capacity, the United States is struggling to keep up with the rest of the world.<sup>119</sup> Commentary has suggested that the FDA could have instituted the 505(b)(2) pathway and provided a framework for follow-on biologics well before the current legislative action.<sup>120</sup> Biologics have already been approved according to structured approval processes in both the EU and Australia.<sup>121</sup>

More importantly, the advance in follow-on biologics approvals abroad has pushed the expansion of the biotech manufacturers in these countries into overtime.<sup>122</sup> This is especially true as "markets . . . are increasingly served by producers in low-cost economies, most notably India and China."<sup>123</sup> For instance, in Singapore, a biotech facility that boasts of being a "[two] million square feet purpose-built biomedical sciences research complex," called "Biopolis," is at ninety-five percent capacity and a phase II construction was set to be completed by the end of 2006.<sup>124</sup>

Two major generic biologic producers from India are poised to

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preventing low income families from receiving proper health care. *See id.* at 581–82.

<sup>117</sup> Saul, *supra* note 35, at A1.

<sup>118</sup> *Id.*

<sup>119</sup> *See* Mary Ann Liebert, Inc., *Should U.S. Approve Follow-on Biologics?*, 25 BIOTECHNOLOGY L. REP., 389, 389–90 (2006).

<sup>120</sup> *See* Mandel, *supra* note 58, at 15–16.

<sup>121</sup> *See Omnitrope*, *supra* note 42.

<sup>122</sup> *See, e.g.,* Fiona Chan, *EDB, Swiss Group to Open \$410M Drugs Plant*, STRAITS TIMES, Feb. 16, 2006, available at 2006 WLNR 2651040.

<sup>123</sup> Alex Scott, *DSM Slashes Pharma Capacity in North America*, CHEMICAL WK., Jan. 11, 2006.

<sup>124</sup> *Companies Leverage Singapore's Research Complex Infrastructure to Reduce Costs and Time-to-Market Facilities*, DRUG WK., May 12, 2006, at 477, available at 2006 WLNR 7656600.

hit a little closer to home.<sup>125</sup> The biologics producers Biocon and Wockhardt were expected to file applications in 2007 to supply the EU with generic insulin, and more generic producers will emerge overseas, perfecting their process for producing generics as the regulations remain stringent in the United States and relax elsewhere.<sup>126</sup> These companies are not alone, as Zenotech Laboratories in Mumbai has received approval for two follow-on biologics to treat cancer.<sup>127</sup> Following its approval for the follow-on drugs, the company expanded its facility in India to meet U.S. FDA and EU standards, perching the company on the edge of follow-on approval in the United States.<sup>128</sup> The company is already in talks with potential partners to “take its G-CSF to the European Union.”<sup>129</sup>

A major issue that is playing out on the world stage involves producers of brand biologics clamoring for the denial of generic producers to use the name of the active compound in the branded biologic.<sup>130</sup> When a traditional generic drug is approved it maintains the same International Nonproprietary Name (INN), which “is crucial for generics’ producers because it gives patients and doctors an instant reference and allows for easy substitution.”<sup>131</sup> Large biotechnology companies are arguing that the effect on the body is not the same with a “bio-similar” because it is not and cannot be the same as the branded drug; biologics are derived from living products and therefore can never be exactly the same.<sup>132</sup>

The FDA has spoken out on this topic and has urged the W.H.O.<sup>133</sup> and European regulators to refuse this proposal by brand producers that are trying to maintain additional product life and prevent substitution at the pharmacy.<sup>134</sup> The FDA maintains that the safeguards in place in the United States against improper substitution are substantial and denying the

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<sup>125</sup> See Saul, *supra* note 35, at A1.

<sup>126</sup> See *id.*

<sup>127</sup> *Zenotech Receives Marketing Approval for Generic GM-CSF, G-CSF*, HINDUSTAN TIMES, Aug. 8, 2006, available at 2006 WLNR 13775138.

<sup>128</sup> See *id.*

<sup>129</sup> *Id.*

<sup>130</sup> Danny Fortson, *Drug Giants Needled By Expensive Name Game*, INDEP. ON SUNDAY, Oct. 8, 2006, at 3, available at 2006 WLNR 17413946.

<sup>131</sup> *Id.*

<sup>132</sup> See *id.*

<sup>133</sup> World Health Organization.

<sup>134</sup> *FDA Urges WHO to Reject Industry Call for Different ‘Biosimilar’ Names*, FDA WK., Sept. 8, 2006, available at 2006 WLNR 15588978.

follow-on biologic the use of the name of the active compound in the drug is unnecessary.<sup>135</sup> This is good news for potential U.S. generic manufacturers because substitution at the pharmacy counter is an integral part of the profitability of the generics industry, along with savings to the customer.

#### V. CONCLUSION—ARE WE BACK AT THE BEGINNING?

The Waxman-Schumer Act provides an abbreviated process for approval of generic biologics, but with the FDA's inability to be decisive, along with the complexity of biologics production leading to a high demand on facilities and struggle to maintain high output cell lines, has the approval process really alleviated the strain on both the price and lag in production of generic biologics? Will the brand name biologic producers merely jump into generic production once their branded drug faces competition? This seems likely. The same companies that produce the branded drug are the companies that are pushing the envelope to develop manufacturing facilities for generic biologics. These are the companies with the know-how and the safety and efficacy data to get the job done.

Furthermore, with the FDA already under funded and struggling to keep pace with new developments, the additional strain of determining comparability may be too much for the FDA to bear, turning it into a "bottleneck."<sup>136</sup> Generic user fees are the proposed answer to this potential problem, by supplementing the budget for the extended amount of time being spent on the project.<sup>137</sup> However, if the FDA were to use the existing safety-ensuring mechanisms, some of this cost could be avoided along with alleviating the problem of bottlenecking by reducing the time spent on applications. The bottlenecking may still occur for the larger molecules that require more safety and efficacy data, but for smaller molecules, time would be saved. For the time being, the FDA seems at a standstill, waiting for the Congress to act and, in their stall, extending the patent on brand-name biologics in favor of the big biotech companies and against consumer interests.

Although the Waxman-Schumer Act is well-intentioned, there

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<sup>135</sup> *Id.*

<sup>136</sup> See *BIO Asserts FDA Needs More Funding to Keep Pace*, CHAIN DRUG REV., Aug. 28, 2006, available at 2006 WLNR 16495512.

<sup>137</sup> *Waxman, Schumer, Clinton Unveil Generic Biologics Bill at 11th Hour*, *supra* note 31.

may not be a significant drop in the cost of biologics, as the traditional generic pharmaceutical industry has experienced, due to the high facility and manufacturing standards of the biologics industry along with the cost of establishing equivalence.<sup>138</sup> Traditional pharmaceuticals experience an average savings of half the cost of the brand-name drug;<sup>139</sup> this savings is the result of utilizing all of the same safety and efficacy information for approval of the follow-on. Add to the cost of extra safety studies the cost of manufacturing facilities for the production of biologics, and the savings diminishes. This is far from the eight to ten billion dollars in savings felt by the public from entry of traditional generic drugs in 1994 alone.<sup>140</sup> The questions that remain are whether the United States can afford to give up a portion of a budding high-tech industry to countries like India and China, and whether there is such a thing as a discount that is not worth the cost.

The Waxman-Schumer Act is poised to at least push the United States into the field of generic biologics; with the push, patients can hope that the biotech industry will be encouraged to support the generic biologics industry. It is said that states would save “hundreds of millions of dollars annually” in Medicaid prescription drug costs<sup>141</sup> and, although the proponents of the bill fail to realize the cost associated with a biologic versus a traditional chemical drug, the United States cannot afford to wait for even a slight savings on biologics. In the end, patients, insurers, and the federal government will realize that the savings may not be what was expected, but any savings is better than the current prohibitive cost of biologics. One thing is certain: the longer brand drug companies can delay an approval process, “the more money they can make.”<sup>142</sup>

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<sup>138</sup> See Linda Loyd, *Opening a Path for Biological Generics*, PHIL. INQUIRER, Sept. 19, 2006, at E1, available at 2006 WLNR 16216321.

<sup>139</sup> GENERIC DRUG ENTRY, *supra* note 17, at 9.

<sup>140</sup> *Id.*

<sup>141</sup> Loyd, *supra* note 138, at E1.

<sup>142</sup> Fortson, *supra* note 130, at 3.

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