

## A Pathway to Follow-On Biologics

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### I. Introduction

Over the past several decades, advances in biotechnology and medicine have created an influx of biologics. Biologics (e.g., insulin, human growth hormone) are complex, protein molecules that are used to treat a variety of ailments. In contrast to chemical drugs (e.g., aspirin, ibuprofen), which are simple, small-molecule compounds easily created by chemists and produced in pill form, biologics are large, complex molecules produced by bioengineered bacteria and other organisms. Biologic products have shown great promise as effective treatments for cancer, autoimmune diseases, and other serious afflictions.<sup>1</sup> Many drug manufacturers, enticed by the promise of patent protection and strong market rates, have entered the field, developing innovative, therapeutic biologics.<sup>2</sup>

Unfortunately, two major factors limit the reach of biologic development: cost and safety. First, the cost of treatment with biologics is expensive and can reach hundreds of thousands of dollars per year,<sup>3</sup> a result of the high cost of development and clinical testing. This cost makes it difficult for many patients to obtain necessary treatment for specific ailments. The benefits of biologics are lost if patients cannot afford to pay for them. Second, safety issues arise from the fact that biologics are larger and more complex than small-molecule drugs, making production, quality control, and quality assurance more difficult. Even small changes in a biologic's manufacture could adversely change its chemical properties and the way it affects individuals.

Competition from generic versions of brand name biologics, known as "follow-on biologics," would address the cost issue by supplying patients with cheaper alternatives as well as providing incentive for generic biologic manufacturers to continue research and development.<sup>4</sup> However, there is currently no legislative framework to address the approval of generic biologics. Under the Public Health Safety Act ("PHSA"), generic biologics must endure the same approval process as the original, reference biologics.<sup>5</sup> The current process for follow-on biologics requires an applicant to duplicate the same type of clinical test cycles that the original, brand name biologic had to go through prior to its approval.<sup>6</sup> Conducting clinical testing for generic biologics is an inefficient use of scarce resources and deters generic biologics competitors from entering the market. An approval process that balances safety and efficacy concerns with the cost and resources of generic biologics is necessary.

Addressing the issues facing biologics becomes even more important when considering the high costs of biologics and a strained healthcare system. Healthcare reform will ultimately

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demand cheaper, affordable biologics. There are already several bills pending in Congress addressing this issue. It is only a matter of time before an abbreviated approval pathway is approved. The need for an approval process for follow-on biologics is heightened by the large number of biologics that will go off-patent in the next several years.<sup>7</sup> It is estimated that \$10 billion worth of biologic drugs will go off-patent by 2010, with an additional \$10 billion going off-patent by 2015.<sup>8</sup>

The process for generic small-molecule drug approval is greatly aided by the fact that a generic drug manufacturer can easily establish that its product and the original are the same.<sup>9</sup> There is currently no comparable approval pathway for generic biologics. The absence of an approval pathway means that generic biologic manufacturers have little incentive to enter a market in which there is a large barrier to entry. Generic manufacturers would have to spend a large amount of money recreating clinical research in order to demonstrate that their generic has the same safety and efficacy as the original. Not only is this not cost-effective, but it also gives brand name manufacturers a de facto extension on their patents. United States patent law protects inventors by giving a patent owner the right to prevent others from using the patent in any manner during its lifetime.<sup>10</sup> A de facto extension of a patent occurs when competitors are unable to develop products until it has expired. This gives the original patent an extra period of protection while competing products are researched, developed, and produced. In the case of generic biologics, generic manufacturers are restricted from conducting comparative clinical trials during the patent life of a pioneer biologic, forcing them to wait for the patent expiration before starting testing.<sup>11</sup> To avoid this, legislation such as the Hatch-Waxman Act has proposed abbreviated approval pathways, permitting companies to use data in ways that would normally be considered patent infringement. This use of data would allow generic drugs to enter the marketplace immediately after the expiration of the original product's patent.

This paper discusses issues that the biologics industry faces today, analyzes bills for abbreviated approval pathways for follow-on biologics currently pending approval in Congress, and proposes several adjustments to those bills. First, this Paper examines why follow-on biologics were not included within the Hatch-Waxman Act. It then discusses the implications of the Hatch-Waxman framework on follow-on biologics and finds that it cannot apply to biosimilars without significant changes to ensure their safety, purity, and potency to match those of the original, reference biologic. In light of the current economy and the high cost of development, manufacturing, and clinical testing, an abbreviated approval pathway for follow-on biologics is the most likely option. Lastly, this paper proposes that a pathway for abbreviated approval should adopt a different standard so as to be more structured than the current proposals before Congress. Any abbreviated approval pathway should require a one year statutory-mandated clinical trial period to ensure the safety of the product. Follow-on biologics should also be required to be "substitutable," requiring a "sameness" between proposed biologics and their respective brand name biologic, as opposed to merely being "similar." Furthermore, I suggest that, while the bills await approval before Congress, the FDA should develop guidelines for approving the generic versions of well-characterized biologics, such as insulin, for which safety is less of a concern because they already have a substantial history of safe use.

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## II. What are Biologics?

According to the PHSA, biologics are a class of biological products derived from living organisms that are used to diagnose, treat, or prevent various medical conditions.<sup>12</sup> Biologics, which are also known as biopharmaceuticals, biologic drugs, or protein drugs,<sup>13</sup> are mostly protein products. They include vaccines, blood and blood components, gene therapy, tissues, and recombinant therapeutic proteins.<sup>14</sup> Originally, biologics were created from purified extracts of animal blood and tissue, but advances in biotechnology have pushed their development toward recombinant DNA technology. This technology consists, essentially, of reprogramming cell lines to mass produce specific biological products.<sup>15</sup> Today the majority of biologics is created by engineering bacterial and yeast cell lines to produce desired proteins.<sup>16</sup> Conventional small-molecule drugs, on the other hand, are derived from chemical compounds and “can be completely characterized on the basis of their chemical structures.”<sup>17</sup>

### A. Biologics as Differentiated from Chemical Drugs

Biologics attain a level of complexity that far outreaches simple molecules and other chemical drugs both structurally and functionally.<sup>18</sup> According to the FDA, most conventional chemical drugs, such as the ones people recognize in their local pharmacies (e.g., Advil®, Tylenol®, and Lipitor®), are created by combining a series of well-defined chemicals in a highly predictable manner to create a product that, despite being created by very different processes, results in an identical final product.<sup>19</sup> Small-molecule, chemical drugs are considered to be chemically, and not biologically, synthesized and usually involve a single, chemical entity.<sup>20</sup> In contrast, proteins comprise the majority of biologic drugs and illustrate the complexity of biologics.<sup>21</sup> Protein products are often too large and complex to be created chemically, which is why scientists insert specific DNA sequences into cells, essentially “programming” bacteria and other living organisms to produce the target biologic.<sup>22</sup>

Structurally, proteins vary widely in size, with some proteins having as few as three amino acids while others have as many as 2,300.<sup>23</sup> Proteins are often much larger than chemical drugs. For example, aspirin has a molecular weight of 180 Da, while the biologic interferon- $\beta$  (used to treat and control multiple sclerosis) has a molecular weight of 19,000 Da.<sup>24</sup> Furthermore, two protein products with identical amino acid sequences can still lack comparable functionality due to differences in their folding patterns, post-translational modifications, and aggregations of subunits.<sup>25</sup> The consequences of subtle differences between proteins with identical amino acid sequences can be significantly dangerous. These dangers were demonstrated by the observed side-effects of Epogen and Eprex, two genetically engineered forms of the human hormone erythropoietin used to treat anemia in patients with chronic renal failure.<sup>26</sup> The specifics of the Epogen and Eprex example are discussed below.

Other differences between biologic drugs and chemical drugs include delivery method, mode of action, and manufacturing methods and costs. While most chemical drugs are administered orally via pill form, biologics are often unstable and easily degrade in the digestive system before reaching the blood stream. Therefore, many biologics must be injected or inhaled in order maximize efficacy within the human body.<sup>27</sup> Biologics can also be “heat sensitive and susceptible to microbial contamination” and must be cared for accordingly, by maintaining their stable storage environments and developing administration methods that preserve their efficacy in the human body.<sup>28</sup> Additionally, a biologic can affect up to 100

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different physiological processes in the body (as opposed to a chemical drug's mere handful of reactions within the body), making it very difficult for researchers to predict physiological responses to specific biologics.<sup>29</sup> Lastly, biologics are much more expensive to develop and manufacture than chemical drugs.<sup>30</sup> Due to the complex and unpredictable nature of biologics, it is crucial that the biologics endure stringent safety review and testing. While chemical drugs only require 40-50 clinical tests, the average biologic requires 250 clinical tests or more.<sup>31</sup> The aforementioned differences between biologics and chemical drugs are why the costs of biologics have risen so sharply over the past couple of decades.

### **B. What are Follow-On Biologics?**

When conventional, small-molecule drugs expire, generic versions of the drugs jump onto the scene, ready to grab a share of the pharmaceutical market. When patent protections and regulatory protections of pioneer biologics expire, companies create follow-on biologics. These are attempts to copy the original biologics and are, in essence, generic versions of the original.<sup>32</sup> However, while generic chemical drugs can be identical to the original, brand name drug, it is virtually impossible to create identical follow-on biologics. Chemical drugs are easy to reproduce because their structures are precisely defined.<sup>33</sup> On the other hand, follow-on biologics are copies of existing biologics made with different cell lines or different manufacturing and purification processes.<sup>34</sup> Using different cell lines and manufacturing techniques will result in a variety of differences between follow-on biologics and pioneer biologics. These disparities are the source of many of the substitutability issues between generic and brand name versions of biologics.

### **C. Problems Currently Facing Biologics**

#### *1. Exorbitant Costs Hamper the Accessibility of Biologic Drugs and Reduce the Incentive for Follow-On Biologics Manufacturers*

The high cost of the research and development necessary to create biologics has driven the cost of receiving these drug therapies to astronomical heights. For example, treatment of breast cancer with Herceptin can cost \$48,000 per year, and treatment of rheumatoid arthritis with Remicade can reach approximately \$20,000 per year.<sup>35</sup> In contrast, the most expensive small-molecule, chemical drug treatment currently on the market costs approximately \$300 per patient per year.<sup>36</sup> Biologics are among the most expensive items in the U.S. healthcare budget.<sup>37</sup> In 2007, Americans spent \$40.3 billion on biologics alone.<sup>38</sup>

Part of the reason behind the rising costs of biologics is that advances in biotechnology have invariably been accompanied by price increases. For example, Fred Banting and Charles Best, the discoverers of insulin, sold the patent for one dollar in an effort to keep it cheap and accessible.<sup>39</sup> The original form of insulin developed by Banting and Best was extracted from pig and cow pancreases and did not last long in the human body. It required significant improvements to lengthen its effectiveness.<sup>40</sup> Yet even such improvements had low accompanying price increases, selling for only \$2.99 a bottle in 1975.<sup>41</sup> However, in 1978, Genentech created the first biologic drug: insulin created by genetically engineered bacteria, which produced insulin biologically instead of chemically.<sup>42</sup> By 1996, the FDA approved the first insulin analogs, which are similar to human insulin but have been genetically manipulated to be slower- or faster- acting.<sup>43</sup> When these improvements hit the market, the price for insulin

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skyrocketed.<sup>44</sup> The cost of insulin to state Medicaid programs in 2005 was \$500 million.<sup>45</sup> At the time of this writing, popular, fast acting versions of insulin like Humalog and Novolog cost upwards of \$60 per bottle.<sup>46</sup> Insulin is only one example of a biologic drug that weighs heavily on the U.S. healthcare system due to high costs.

## 2. *Safety Issues Inherent Within Biologics*

Biologics are much larger and more complex than conventional, chemically-produced, small-molecule drugs. Even slight changes in manufacture can greatly affect the biological composition of the product and, subsequently, their safety and efficacy in patients.<sup>47</sup> Differences in protein configurations may occur because of the environmental conditions in which a biologic is manufactured and will have correspondingly different effects on individuals.

The major safety concern with biologics is immunogenicity. Immunogenicity occurs when the body develops an allergic response to properties intrinsic to the biologic.<sup>48</sup> The allergic reaction occurs because biologics are created in cells of other organisms, and the human body will often view them as foreign substances resulting in an immune response and accompanying antibody production.<sup>49</sup> In some instances, the immune response can be so severe that patients become allergic to even natural proteins formed by their own bodies, possibly worsening their conditions.<sup>50</sup>

Unlike processes used for creating generic chemical drugs, for which the products can be confirmed as identical to the brand name drug in terms of structure, safety, and efficacy despite differing manufacturing methods, it is nearly impossible to determine whether follow-on biologics and their pioneer biologic counterparts share the same effectiveness and quality. Of particular concern is the fact that the complexity of proteins opens biologics up to a varying danger of immunogenicity. For example, two proteins with the same structure but slightly different production methods resulted in the discovery of Epogen and Eprex. The biologic drugs Epogen and Eprex are both agents used to treat patients suffering from anemia (low red blood cell counts) due to kidney failure or due to side effects from treatments such as chemotherapy.<sup>51</sup> Epogen and Eprex use the same active ingredient: a man-made form of the protein erythropoietin, called epoetin alfa. Epogen was prescribed to patients in the U.S. while Eprex was prescribed to patients elsewhere around the world, particularly in Europe.<sup>52</sup> They were both produced using the same recombinant DNA technology and had identical amino acid sequences, but because of slight differences in the way each biologic was manufactured the resultant drugs caused very different reactions in their respective patients.<sup>53</sup> Epogen was created in human serum albumin while Eprex was made in glycine and polysorbate 80.<sup>54</sup> It is still unknown what factors were exactly responsible, but the resulting changes in Eprex were sufficient to change its immunogenicity, causing patients to develop pure red cell aplasia (PRCA), a syndrome characterized by “anemia, low reticulocyte count, absence of erythroblasts on bone marrow, resistance to epoetin therapy, and antibodies for erythropoietin.”<sup>55</sup> Simply put, patients taking Eprex began producing antibodies at much higher rates than patients taking Epogen.<sup>56</sup> The patients experienced an allergic reaction to epoetin so severe that they also became allergic to the epoetin their bodies produced naturally. The biologic, originally taken to improve a patient’s medical condition, effectively made them more ill. From 1988 to 1998, pure red-cell aplasia was reported in three patients who had undergone treatment with

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Epogen.<sup>57</sup> After the release of Eprex in Europe and between January 1998 and April 2004, researchers discovered 175 cases of epoetin-associated pure red-cell aplasia related to Eprex, but only 5 cases related to Epogen.<sup>58</sup> Opponents to abbreviated approval pathways for follow-on biologics often cite this case as proof of the dangers arising from biologics that, although seem the same, have clearly different pharmacological effects.

The soaring prices of biologics are forcing the U.S. to spend millions of additional dollars on healthcare. As a result, there is a demand for generic biologics because of the exorbitant cost of buying branded biopharmaceuticals. At the moment, generic biologic drug manufacturers have no economic incentive to enter the field of follow-on biologics. The possibility for a reasonable return on investment is too low to risk investing in expensive clinical trials, safety tests, and waiting for FDA approval. However, in light of the number of bills pending before Congress and the looming healthcare crisis in America, it is only a matter of time before Congress approves an abbreviated approval pathway for follow-on biologics. The current bills, however, are insufficient and should be adjusted to properly accommodate for and balance the needs and concerns of all parties involved.

### **III. FDA Regulatory Scheme for Brand Name and Generic Drugs, and for Pioneer and Follow-On Biologics**

The FDA regulates new drugs and biologics for approval and licensure.<sup>59</sup> Small-molecule drugs are regulated under the Food, Drug and Cosmetics Act (“FDCA”).<sup>60</sup> However, biologics are regulated under both the Public Health Service Act (“PHSA”) and the Food, Drug and Cosmetics Act (“FDCA”). The FDCA applies to biologics because they fall within the FDCA definition of “drugs.”<sup>61</sup>

#### **A. The Approval Process for Small-Molecule Drugs**

The pre-clinical phase of developing a drug usually begins with basic discovery and research in various academic, government, and industry laboratories. After extensive testing on animal models, the applicant for a drug can file an Investigational New Drug (“IND”) application.<sup>62</sup> After the FDA evaluates the IND and grants permission for the applicant to conduct clinical studies on humans, the clinical phase of testing begins.<sup>63</sup>

There are three phases of clinical trials: Phase I clinical trials involve a small group (twenty to one hundred) of healthy volunteers to determine whether the drug is safe and effective; Phase II clinical trials then test the drug on a larger pool of patients (several hundred) with the specific intention of confirming that the compound has the intended effect, at which point the drug ultimately moves on to Phase III. Phase III, which is “the most costly stage of drug development,” involves several thousand patients and evaluates the safety and effectiveness of the drug.<sup>64</sup> At this point, approximately 64% of the drugs in Phase III clinical testing are submitted as New Drug Applications (NDAs) and new Biologic License Applications (BLAs) to the FDA.<sup>65</sup> Biologic License Applications will be discussed further below. Until this point, the developmental and research costs of biologics and small-molecule chemical drugs are comparable. The average cost of bringing a small-molecule drug to market varies from \$800 million to \$1.7 billion while the average cost for a biologic drug is \$1.2 billion.<sup>66</sup> Once the FDA approves the new product, the drug name and related patent information is published in the Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”).<sup>67</sup>

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## **B. The Hatch-Waxman Act: An Accelerated Approval Pathway for Generic Small-Molecule Drugs**

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration (“Hatch-Waxman Act”), which amended the Food, Drug, and Cosmetic Act in a successful bid to stimulate generic competition and balance the needs of competing interests in the pharmaceutical industry.<sup>68</sup> The Hatch-Waxman Act was Congress’s response to the outcome of *Roche Products, Inc. v. Bolar Pharmaceutical Co.*,<sup>69</sup> in which the Federal Circuit held that the generic firm infringed on a brand name sleeping pill when they began experimenting with the original, patented product in order to satisfy FDA testing requirements. The court found that the generic’s use was for “business reasons and not for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.”<sup>70</sup> Congress enacted the Hatch-Waxman Act to reverse the holding in *Roche Products* by specifically exempting the manufacture, use, or sale of a patented invention from being liable for infringement when use was reasonably related to generating data for regulatory approval (also known as the “271(e)(1) exception”).<sup>71</sup>

Under Hatch-Waxman, generic drug applicants are not required to conduct clinical testing of drugs that have already been proven to be safe and effective.<sup>72</sup> Instead, the applicant only needs to demonstrate that the generic drug product is the equivalent of the brand name drug, in effect, piggybacking off the brand name drug’s research and assurances of safety and effectiveness.<sup>73</sup> This regulatory scheme has “reduced prescription drug prices, increased access for more Americans [to needed pharmaceuticals], and hastened the pace of innovation.”<sup>74</sup>

There are two “shortcuts” offered by the Hatch-Waxman Act: the abbreviated new drug application (“ANDA”, also known as the 505(j) application), and the 505(b)(2) pathway.<sup>75</sup> The ANDA pathway allows drugs that are “identical or almost identical” to rely on previously submitted NDA information of the brand name drug as their reference material without necessitating clinical studies or other proof of findings of safety and effectiveness.<sup>76</sup> On the other hand, the 505(b)(2) pathway also allows reliance on the reference drug’s approved NDA data, but instead of requiring that the two molecules be identical, the 505(b)(2) pathway permits the application of drugs that are merely “similar” and not necessarily “identical” (e.g., a drug with the “same composition but different proposed use than the brand [name] drug”).<sup>77</sup>

This Act also gives the first generic drug applicant to file a “first-to-file” exclusivity for the first 180 days. This means that for six months after the expiration of the brand name drug, the FDA will not look at or approve of any other ANDAs.<sup>78</sup> This creates incentive for generic drug manufacturers to enter the market by being the first to file. In this manner, the FDA effectively limits the market to two players by refusing to allow any other ANDAs for that period of six months.

## **C. The Approval Pathway for Pioneer Biologics and Follow-On Biologics**

As discussed earlier, a BLA is an application to obtain a license to market a biologic. It must demonstrate that “the biological product . . . is safe, pure, and potent; and the facility in which the biological product is manufactured, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent . . . .”<sup>79</sup>

Twenty-five years after the enactment of the Hatch-Waxman Act, there is still no equivalent approval process for biologics. In fact, in order to obtain FDA approval, follow-on biologics must endure the same testing and clinical trials as the original biologics in order to determine

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their safety and efficacy.<sup>80</sup> Essentially, manufacturers of new biologic products must apply for approval as if their product was an entirely new drug rather than a generic equivalent of a preexisting, pioneer biologic. The Hatch-Waxman Act specifically does not address biologics for several reasons. When the Act was pending before Congress in 1984, technology was ill-equipped to handle the complexities of demonstrating equivalence and safety in follow-on biologics. Legal analysis of the Act's legislative history reveals that in order for the abbreviated pathway created by the Act to be applicable, both the pioneer drug and the generic must be chemically identical molecules.<sup>81</sup> The Hatch-Waxman Act emphasizes the importance for determining that brand name and generic versions of small-molecule chemical drugs are bioequivalent to one another. Since it is extremely difficult to demonstrate bioequivalency between two biologic products, the abbreviated approval process for chemical drugs is inapplicable to biologics.

#### **IV. The European Union Has a Regulatory Scheme in Place for an Abbreviated Approval Process for Biosimilars**

A regulatory pathway for biosimilars has been in place in the European Union ("E.U.") since 2003.<sup>82</sup> E.U. legislation has declared that the final decision to approve or reject a drug fell on the European Commission (the European version of the FDA) and has mandated comparative clinical trials, one year of testing, and risk-management plans.<sup>83</sup> European biosimilar manufacturers can claim that their drug is "similar" to existing biologics by "comparing the quality, safety, and efficacy of the new drug to the biologic," and ensuring that the biosimilar and the original biologic have comparable immunogenicity.<sup>84</sup>

The E.U. is acutely aware of the dangers and disastrous consequences of unpredictable immunogenicity after the tragic incidents associated with Eprex®. With the dangers of immunogenicity fresh in mind, the E.U. passed legislation for an abbreviated regulatory pathway for biosimilars that compares the quality, safety, and efficacy of the biosimilar applicant.<sup>85</sup> Most importantly, the applicant must show that the pioneer biologic and the proposed biosimilar share comparable immunogenicity, a requirement that often involves preclinical and clinical testing.<sup>86</sup> Since the E.U. passed this legislation, the European Commission has approved two different generic human growth hormones, Omnitrope and Valtropin.<sup>87</sup> Other countries have since followed suit, with Japan being the most recent country to implement a set of follow-on biologic guidelines to accompany its previously established accelerated drug approval system.<sup>88</sup>

#### **V. The U.S. Currently has Several Bills Proposing Abbreviated Approval Pathways for Follow-On Biologics**

Generic biologics manufacturers and local governments are insisting upon legislation to create an abbreviated approval process as well as a regulatory pathway for follow-on biologics.<sup>89</sup> Congress has responded by proposing several bills for abbreviated approval pathways that are currently pending. Representative Henry Waxman (D-CA) of Hatch-Waxman fame remarked at the Biosimilars 2007 Conference on September 24, 2007, that "[b]iotech drugs are the future of medicine."<sup>90</sup> He is standing behind his statement by drafting and supporting the bill entitled the "Promoting Innovation and Access to Life-Saving Medicine Act" (H.R. 1427) (hereinafter referred to as "Waxman's Bill").<sup>91</sup> Another bill standing before the

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House is the “Pathway for Biosimilars Act” (H.R. 1548), which was introduced by Representative Anna Eshoo (D-CA) (hereinafter referred to as “Eshoo’s Bill”).<sup>92</sup> Both Bills are discussed below.

**A. Waxman’s “Promoting Innovation and Access to Life-Saving Medicine Act” (H.R. 1427)**

After its success, the Hatch-Waxman Act of 1984 is a natural reference for creating a regulatory pathway for follow-on biologics.<sup>93</sup> Rep. Waxman introduced the “Promoting Innovation and Access to Life-Saving Medicine Act” on March 11, 2009, and this bill bears many similarities to the Hatch-Waxman Act.<sup>94</sup> For example, Waxman’s Bill follows the timeline of the Hatch-Waxman Act by proposing similar exclusivity periods, and not requiring clinical trials.<sup>95</sup> Instead of conducting clinical trials, Waxman’s Bill would allow follow-on biologic applicants to rely upon the safety and efficacy data of the reference biologic, much like the Hatch-Waxman Act allows generic drugs to piggyback off brand name drugs’ test data.<sup>96</sup> Furthermore, Waxman’s Bill mandates that follow-on biologic applicants must demonstrate interchangeability with the brand name biologic.<sup>97</sup>

Waxman’s Bill departs slightly from the Hatch-Waxman Act by giving a 180 day period of first-to-file exclusivity after the first sale or a full year after the approval of the first follow-on biologic found to be interchangeable with the original biologic (the Hatch-Waxman Act only gives a 180 exclusivity period.)<sup>98</sup> This exclusivity provision for first-to-file applicants prevents the FDA from approving a similar biologic product for sale to the public for a period of time after the introduction of the first follow-on biologic.

A separate exclusivity period is also provided for the reference biologic manufacturer. Waxman’s Bill follows in the footsteps of the Hatch-Waxman Act and provides pioneer biologic manufacturers with a five year data exclusivity period. The FDA cannot approve any generic versions of the biologic during this period.

**B. Eshoo’s “Pathway for Biosimilars Act” (H.R. 1548)**

Although both Eshoo’s Bill and Waxman’s Bill purportedly share the same goal of finding a mechanism for the accelerated approval of follow-on biologics, the two bills are substantially different. On March 17, 2009, Reps. Anna Eshoo, Jay Inslee, and Joe Barton introduced their version of a follow-on biologics bill, entitled the “Pathway for Biosimilars Act” (H.R. 1548).<sup>99</sup> According to the press release, the bill “sets forth a straightforward, scientifically based process for expedited approval of new biologics based on innovative products already on the market.”<sup>100</sup> Eshoo’s Bill leans heavily toward incentivizing brand name developers to continue developing innovative drugs by providing lengthy exclusivity periods. While Waxman’s Bill gives original biologic manufacturers a five-year period exclusivity, Eshoo’s Bill mandates at least 12 years of data exclusivity (extendable up to 14.5 years) for pioneer biologics.<sup>101</sup> On the other hand, Eshoo’s Bill also allows for a longer period of exclusivity for generic biologics, awarding up to two years of market exclusivity to the first follow-on biologic found to be interchangeable with the original product.

Eshoo’s Bill further requires that a generic biologic applicant establish that the proposed product is “biosimilar” to the reference biologic. Each follow-on biologic applicant must complete a period of clinical trials comparing the immunogenicity of the applicant’s product

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with the original biologic. Analytical studies must show that the proposed biological product is highly similar in toxicity, safety, purity, and potency.

### **C. Exclusivity Periods**

The provisions in Waxman's and Eshoo's Bills that generate the most attention in interested parties are the exclusivity periods. The bills provide for two exclusivity periods: (1) for the first-to-file follow applicants, preventing the FDA from approving similar follow-on biologic applicants for a specified period of time after the introduction of the first follow-on biologic applicant, and (2) for pioneer biologics, allowing for a period of data exclusivity that prevents the FDA from approving any follow-on versions of the biologic until the period has expired. The exclusivity period for first-to-file applicants acts as an incentive for generic biologic developers by creating a two-entity market. This reduces competition and allows for a higher profit margin. The exclusivity period for pioneer biologics promotes continued innovation and acts as a mitigation factor, providing the original biologic with the time lost due to the wait for FDA approval. The exact length of each exclusivity period has been analyzed and debated extensively. Extensive research has been conducted to determine the optimal length of time for extensions and various other economic aspects of biotechnology.<sup>102</sup> Earlier this year, the White House has voiced an opinion on this matter by sending a letter to Rep. Waxman recommending a seven year data exclusivity period for pioneer biologics.<sup>103</sup>

## **VI. Proposal**

The generic biologic approval framework that this paper proposes aims to balance the safety concerns of biologic drugs against the need for an accelerated approval process. It is imperative that any regulatory pathway balance the needs of the pioneer biologic developers, follow-on biologic manufacturers, and the American public. The current bills pending approval in Congress are heading in the right direction, but still need refinement.

### **A. Inevitability: It is Only a Matter of Time Before an Abbreviated Approval Pathway is Approved**

The purpose of creating an abbreviated approval pathway for follow-on biologics is to stimulate generic competition while simultaneously providing incentives for innovation. Brand name companies and other industry opponents of developing this pathway argue that the reason biologic drugs were not originally included in the Hatch-Waxman framework was because of the difficulty of characterizing biologics to ensure equivalency.<sup>104</sup> First, the opponents of creating an abbreviated approval pathway must recognize that the creation of such a regulatory pathway is just a matter of time. The rising costs of biologics has already put a strain on the U.S. healthcare system, creating a pressing need for cheaper biologics, especially in light of the recent economic environment, and the best solution for the cost problem is promoting the availability of generic biologics. In order to offset the costs that inherently make biologics expensive to develop and manufacture and in order to incentivize generic drug manufacturers to enter the follow-on biologics arena, an abbreviated approval system is the best approach. Second, the inadequacy of scientific knowledge, which opponents often cite, may have been a legitimate concern in 1984 when the Hatch-Waxman Act was first approved by Congress, but scientific progress over the past twenty-five years has advanced technology

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sufficiently that current techniques permit follow-on biologic product manufacturers to accurately assess their products for comparability with brand name products.<sup>105</sup> While there is no single method that is capable of establishing the comparability of biologics on its own, there are now many analytical technologies that can be used to confirm protein configuration.<sup>106</sup> Such technologies include orthogonal protein purification, hyphenated mass spectrometry, isoelectric focalization, and SDS-PAGE.<sup>107</sup>

#### **B. Immunogenicity Mitigated as a Concern by Imposing a Required One-Year Clinical Study Period**

The biggest concern regarding a regulatory pathway for follow-on biologics is, of course, safety—specifically, immunogenicity. The often cited example of the dangers of follow-on biologics is the immunogenicity caused by Eprex. Recent research has found, however, that the increased incidence of pure red cell aplasia with Eprex may be due to its manufacture using uncoated rubber stopper syringes (i.e., immunogenicity caused by the packaging of the biologic rather than the biologic itself).<sup>108</sup> According to a group’s research results, “[a] technical investigation identified organic compounds leached from uncoated rubber stoppers in prefilled syringes containing polysorbate 80 as the most probable cause of the increased immunogenicity.”<sup>109</sup> As such, this example illustrates that the purported dangers of biologics does not necessarily exist only in biologics, but may be a possibility in any manufactured drug.

Nevertheless, it is evident that some clinical testing should be required to ensure public safety. Waxman’s Bill removes the clinical trial requirement completely from the table, allowing the follow-on biologic to completely rely on the pioneer biologic’s clinical research data. Prudence requires that a period of clinical testing still be performed on follow-on biologics. Although advances in technology have made it so that a “follow-on protein product is likely to meet the requisite standards for identity, potency, purity, quality, and safety,”<sup>110</sup> biologics are, as mentioned above, still extremely complex molecules.

Therefore, I propose that the abbreviated approval pathway require a one year period of clinical trials. Europe currently mandates a one year clinical trial period to demonstrate comparability between biosimilars and pioneer biologics. The E.U. is wary of approval pathways for follow-on biologics because of issues identified with the introduction of Eprex, and yet they assert that a one year clinical trial period is sufficient. I believe that the U.S. should follow suit and require a one year period of clinical trials in order to establish follow-on biologics’ safety.

Waxman’s Bill completely discards the requirement for clinical trials altogether.<sup>111</sup> This is unwise in light of the complex nature of biologics and the fact that creating and guaranteeing follow-on biologics to be identical in every way to their reference biologic is nearly impossible. Despite the fact that technology now allows for better characterization of biologics, the possibility of immunogenicity is still present. Eshoo’s Bill requires clinical trials to determine the immunogenicity of proposed follow-on biologics, but the language of the bill does not give a minimum requirement for clinical trials. This gives too much discretion to the FDA, and although the FDA has its own set of regulations to ensure safety, a minimum requirement for a period of clinical testing will only aid in ensuring the safety of follow-on biologics.

Thus, a one year clinical trial period would help protect consumers from safety concerns stemming from biological products, such as varying immunogenicity. As discussed above, we

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should look comparatively at foreign systems when determining what period of time would be effective and efficient. The E.U. is an ideal model for the United States because drug patents in Europe tend to expire earlier than those in the U.S., and European manufacturers have already begun to seek approval for biosimilars.<sup>112</sup> Experience with creating an abbreviated approval pathway for biosimilars in Europe can therefore be a model from which the United States can develop its regulatory system.

### **C. Language for Follow-On Biologics Must Ensure that They are “Substitutable” Rather Than Merely “Biosimilar”**

Any approval pathway for follow-on biologics, regardless of whether it is abbreviated or not, must require that the applying biologic be held to a higher, “substitutable” standard. This would require the applicant to demonstrate that the incoming drug demonstrates a “sameness” with respect to its reference biologic. The interchangeability and therapeutic equivalence of biologics cannot be based on the same standards and criteria used for comparing small-molecule chemical drugs. While it is widely accepted that two drugs consisting of the same chemical structure are sufficiently equal counterparts, the complexity of protein synthesis makes it improbable that two products made with differing processes can be considered equal. Therefore it is imperative that a new standard for comparability between biological products be established. The FDA has found that large protein products with similar compositions may behave markedly different in different individuals and could result in cases of immunogenicity or adverse side effects.<sup>113</sup>

The language of any proposed legislation is critical in ensuring that future follow-on biologics are as safe, effective, and reliable as the original biologic they are based upon. Inadequate definitions in the language of the bill may also lead to confidence issues among physicians. If follow-on biologics are merely labeled as “highly similar,” doctors may be more reluctant to prescribe generic versions of the biologic, which would defeat the cost-saving goals of follow-on biologics. By specifically defining “substitutable” to mean a higher standard to which follow-on biologics must satisfy, both doctors and patients can be assured a safer product. However, to have a “substitutable” standard would require a clear definition of what is “substitutable” versus what is merely “highly similar.” This section examines the proposed bills’ definitions and requirements for comparability between follow-on and pioneer biologics and then introduces a different standard for comparability that emphasizes follow-on biologics’ substitutability with the original biological product.

Waxman’s Bill allows an applicant to rely on the data from the reference biologic in applying for approval as long as the applicant can show “that the biological product and the reference product contain highly similar molecular structural features.”<sup>114</sup> The proposed biologic must be “biosimilar” meaning that it is interchangeable with the reference biologic.<sup>115</sup> According to the bill, a product is “biosimilar” if there are “no *clinically meaningful* differences between the biological product and the reference product . . . in terms of the safety, purity, and potency.”<sup>116</sup> If a patient’s treatment demands that a biologic be administered more than once, the proposed follow-on biologic must allow a patient to be able switch between the brand name and generic versions of the biologic “without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, compared to the expected risks from continuing to use the reference product without such

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switching.”<sup>117</sup> Once more, the wording of “clinically meaningful differences” is unclear as it currently stands in the Bill. The ambiguity of the definition would allow too much room for variability between follow-on and original biologics.

On the other hand, Eshoo’s Bill is less lenient than Waxman’s Bill with regard to proof of similarity. It requires that the follow-on biologic applicant must show that “the biological product . . . is biosimilar to the reference product and any biological product licensed . . . that has been determined to be interchangeable with the reference product; and can be expected to produce the same clinical result as the reference product . . .”<sup>118</sup> and can be used interchangeably with the reference product in situations where the biologic product must be administered more than once to a patient.<sup>119</sup> Interchangeability is therefore based on whether a proposed product is “biosimilar” to the original product at the Secretary of Health and Human Services’ discretion.

Both Waxman’s and Eshoo’s Bills focus on using the vaguely defined term “interchangeability” of biologics instead of looking toward determining their sameness. The Bills would permit molecular differences between proposed follow-on biologics and pioneer biologics, allowing for increased safety risks to patients. The definition of “substitutable” should be one that requires a proposed follow-on biologic and a pioneer biologic to be the *same* with regard to their immunogenicity, safety, quality, and efficacy.

Ultimately an abbreviated approval pathway should provide strict, statutory rules as to the length of the clinical trial period, the exclusivity periods, and the various specifics that ensure a safe but cost effective product.

#### **D. The FDA Should Set Up Guidelines for Well Characterized Follow-On Biologics**

In addition to the statutory guidelines, the FDA should set up guidelines for approving follow-on versions of well-known biologics such as insulin. Insulin, as well as improvements made on it, has been around for a long time, and its patent expired years ago.<sup>120</sup> The number of diabetics is growing in this country, and healthcare providers and government officials are eager to find cheaper alternatives to insulin.<sup>121</sup> The same applies to human growth hormones.<sup>122</sup> Because insulin and growth hormones were approved originally as regular drugs, the FDA now “has the legal authority to approve generic versions.”<sup>123</sup> Approval by the FDA would be faster and would be able to address health and cost concerns almost immediately, instead of waiting for the undeterminable for Congress to implement an abbreviated approval pathway. In 2001, the FDA began developing regulatory advice for companies seeking to make follow-on biologic versions of insulin and human growth hormone, but has recently delayed final guidelines.<sup>124</sup>

In fact, the FDA has approved a generic biologic drug in the past: Omnitrope, a recombinant growth hormone used for treating “pediatric patients who suffer growth failure and adults with growth hormone deficiency.”<sup>125</sup> Omnitrope was originally filed as an NDA, and for a period of time the FDA kept trying to defer making a decision on Omnitrope. When it was ultimately forced to make a decision, the FDA approved Omnitrope under the 505(b)(2) pathway mentioned *supra*.<sup>126</sup> It based its approval of Omnitrope on a finding that Omnitrope was “sufficiently similar” to Pfizer’s Genotropin.<sup>127</sup> The FDA was able to do this because Omnitrope is not very complex, it has a “long and well documented history of clinical use,” and there was already existing information about its pharmacokinetic properties, and this

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information allowed the FDA to establish similarity to Genotropin without relying on “chemistry, manufacturing, and control . . . data.”<sup>128</sup>

The FDA cautioned against expecting that all follow-on versions of a biologic following this path would be approved, and it is true that not all generic versions of biologics necessarily should go through the 505(b)(2) pathway for approval. But where a biologic such as insulin is well known and fully characterized, safety is no longer in contention and rising costs greatly outweigh the safety concerns. The best course of action would be for the FDA to have guidelines for speeding up the approval of these follow-on biologics.

## VII. Conclusion

Biologics are rapidly growing in importance in the medical world. The ability of biopharmaceutical drugs to replace natural proteins produced by the body make them invaluable as therapy regimens to target major disease including cancer, infectious agents, and a variety of other health conditions. However, the immense cost of treatment with biologics can reach hundreds of thousands of dollars a year, an expense that puts treatment out of reach for many patients who could potentially benefit. The costs of biologics are also impacting the current healthcare crisis, and therefore the arrival of an abbreviated approval process for follow-on biologics is inevitable and must be both examined and discussed.

Consideration of the current drug approval system (the Hatch-Waxman Act) and the available options for a regulatory pathway for generic biologics (Waxman’s and Eshoo’s Bills) reveals that the bills currently pending before Congress still need revision. Specifically, the bills should include a statutory requirement for a one year clinical trial period to examine the immunogenicity and ensure the safety of follow-on biologics. Also, follow-on biologics should be held to a higher, “substitutable” standard when being compared with the original brand biologics, requiring that the follow-on biologic be sufficiently the “same” as the original, pioneer biologic. Additionally, while the bills before Congress await approval, the FDA should set up guidelines to allow for the approval of follow-on versions of well known biologics such as insulin and human growth hormone whose patents have already passed expiration. Considering the importance of biologics as a growing field of medicine that treats many medical ailments, Congress should ensure an abbreviated approval process for follow-on biologics. An abbreviated process with a mandatory one year clinical testing period that requires a follow-on biologic to be the same as its reference biologic would be the best option to address the issues currently facing biologics.

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1. N. Lee Rucker, *Biologics in Perspective: Expanded Clinical Options Amid Greater Cost Scrutiny Fact Sheet*, AARP Public Policy Inst., June 11, 2007, [http://www.aarp.org/health/drugs-supplements/info-2007/fs136\\_biologics.html](http://www.aarp.org/health/drugs-supplements/info-2007/fs136_biologics.html).

2. Fed. Trade Comm’n, *Emerging Health Care Issues: Follow-on Biologic Drug Competition* 3 (June 2009), available at [http://www.ftc.gov/os/2009/06/P083901\\_biologicsreport.pdf](http://www.ftc.gov/os/2009/06/P083901_biologicsreport.pdf)

3. Ingrid Kaldre, *The Future of Generic Biologics: Should the United States “Follow-On” the European Pathway?*, 9 DUKE L. & TECH. REV. 1, 4 (2008).

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4. Brand-name biologics are often called “pioneer” or “branded” biologics, and these terms are used interchangeably. When used in context with generic biologics, pioneer biologics are also referred to as “reference” biologics because they provide the reference from which the generic biologics are developed. The Federal administrative agencies in the U.S. refer to generic biologics as “follow-on biologics,” while the European Union uses the term “biosimilars.” Both terms refer to the same thing, but this Paper will use the term “follow-on biologics” for generic biologics in the United States and “biosimilars” when addressing generic biologics in the E.U.

5. AARP Public Policy Institute, *supra* note 1, at 3.

6. Gregory N. Mandel, Note, *The Generic Biologics Debate: Industry’s Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 1, 23 (2006).

7. *See id.* at 4–5. Sixteen of 27 of the top-selling biologic products comprising approximately 87 percent, or \$112 billion worth, of today’s total global value of the biologics industry were approved before 2000 and are now set to expire by the year 2014. *Id.*

8. Rachel Chu & Meir Pugatch, *Biogenerics or Biosimilars? Discussing the Present, Considering the Future*, Stockholm Network, [http://www.stockholm-network.org/downloads/publications/Biosimilars\\_FINAL.pdf](http://www.stockholm-network.org/downloads/publications/Biosimilars_FINAL.pdf) (2009).

9. Alan J. Morrison, *Biosimilars in the United States: A Brief Look at Where We Are and the Road Ahead*, 26 BIOTECHNOLOGY L. R. 463, 465 (2007).

10. All patents with a filing date after June 8, 1985, have a patent period of 20 years from the date of filing. Patents filed in the United States prior to that date have a patent period of 17 years from the patent’s date of issue. 35 U.S.C. § 154 (2002).

11. Under the Hatch-Waxman Act, generic drug makers can use brand name drugs in clinical trials that would otherwise be considered patent infringement provided that the use is related to obtaining FDA approval. To preserve the incentive for brand name companies to continue their research and to compensate for time lost due to waiting for FDA approval, the Act allows for de facto extensions under certain circumstances. Fed. Trade Comm’n, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 4* (2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

12. 42 U.S.C. § 262(i) (2009), Dept. of Homeland Security Revocation of Notice, 7 C.F.R. § 205.2 (2009).

13. The Public Health Service Act (“PHSA”) uses the term “biologics” when referring to biological products. However biologics go by many other names. Terms such as “biopharmaceuticals,” “biologic drugs,” and “protein product” are used interchangeably in the literature addressing these issues.

14. Food and Drug Administration, *About FDA: What Are “Biologics” Questions and Answers*, <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133077.htm> (last visited October 30, 2009). (hereinafter FDA, *What Are “Biologics”*).

15. Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, 2009 B.C. INTELL. PROP. & TECH. F. 070201, July 19, 2009, at 6.

16. *Id.* at 6–7.

17. Scott Gottlieb, *Biosimilars: Policy, Clinical, and Regulatory Considerations*, 65 AM. J. HEALTH-SYS. PHARMACY, no. 14, at S4 (Supp. 6 July 15, 2008).

18. Morrison, *supra* note 9, at 465.

19. *Why is Patient Safety A Concern in the Biosimilars Debate?*, BIOTECHNOLOGY INDUSTRY ORG., <http://www.bio.org/healthcare/followonbkg/PatientSafety.asp> (last visited December 15, 2009).

20. FDA, *supra* note 14.

21. Sahr, *supra* note 15, at 7.

22. *Id.* at 10.

23. *Id.* at 8.

24. Michał Nowicki, *Basic Facts about Biosimilars*, 30 KIDNEY & BLOOD PRESSURE. RES. 267, 268 (2007), available at <http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=000105133>.

25. *See id.* Amino acids are the building blocks of proteins. A protein is made of one or more strands of amino acids, also known as polypeptides, that has folded in on itself based on the hydrophobic and hydrophilic interactions of each amino acid’s specific side chains. *See* J. Stein Carter, *Amino Acids and Proteins*, U. CINCINNATI, <http://biology.clc.uc.edu/courses/bio104/protein.htm> (last modified Nov. 2, 2004). Depending on the pH, temperature, and other environmental factors, the polypeptides that make up a protein may react and correspondingly fold into other configurations or, in some instances, denature and completely lose its original configuration.

26. EPOGEN, <http://www.epogen.com> (last visited November 5, 2009).

27. Kaldre, *supra* note 3, at 10.

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28. FDA, *supra* note 14.
  29. Nowicki, *supra* note 24, at 267.
  30. Kaldre, *supra* note 3, at 15.
  31. *Id.* at 14.
  32. Nowicki, *supra* note 24, at 268.
  33. *Id.*
  34. *Id.*
  35. Kaldre, *supra* note 3, at 14.
  36. Zach Patton, *Complex Rx*, GOVERNING MAG., Oct. 2007, at 58.
  37. Megan Thisse, *Working the Bugs Out of Biologics: A Look at the Access to Life-Saving Medicines Act and Follow-On Biologics*, 18 ALB. L.J. SCI. & TECH. 543, 563 (2008).
  38. *Id.*
  39. Linda von Wartburg, *Why Does Insulin Cost More Than Ever? It's All in the Way It's Made*, DIABETES HEALTH, June-July 2007, at 42, available at <http://www.diabeteshealth.com/read/2007/05/23/5206/why-does-insulin-cost-more-than-ever-its-all-in-the-way-its-made/>.
  40. *Id.*
  41. *Id.*
  42. *Id.*
  43. *Id.* at 43.
  44. *Id.*
  45. Thisse, *supra* note 37, at 563.
  46. John Walsh & Ruth Roberts, *Humalog and Novolog Insulins*, DIABETES NET.COM, [http://www.diabetesnet.com/diabetes\\_treatments/insulin\\_humalog.php](http://www.diabetesnet.com/diabetes_treatments/insulin_humalog.php) (last visited Dec. 18, 2009).
  47. BIOTECHNOLOGY INDUSTRY ORGANIZATION, *Why is Patient Safety a Concern in the Biosimilars Debate?*, <http://bio.org/healthcare/followonbkg/PatientSafety.asp> (last visited Nov. 5, 2009).
  48. ALSTON + BIRD LLP, *Health Care Advisory: Primer on Generic Biologics* (Nov. 20, 2006), <http://www.alston.com/> (search for "generic biologics"; then follow "Biogenerics Primer FDA Advisory" hyperlink).
  49. Gottlieb, *supra* note 17, at S5.
  50. See Charles L. Bennett et al., *Pure Red-Cell Aplasia and Epoetin Therapy*, 351 NEW ENG. J. MED. 1403, 1404 (2004), available at <http://content.nejm.org/cgi/content/full/351/14/1403>. (last visited November 5, 2009) (incidents of pure red-cell aplasia due to treatment by the biologics Epogen, Eprex, and NeoRecormon, an epoetin beta formulation.)
  51. U.S. FOOD AND DRUG ADMINISTRATION, *FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen and Aranesp*, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm> (last updated Apr. 8, 2010).
  52. Charles L. Bennett et al., *Long-Term Outcome of Individuals with Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Epoetin: A Follow-Up Report from the Research on Adverse Drug Events and Reports (RADAR) Project*, 106 BLOOD 3343, 3344 (2005), available at <http://bloodjournal.hematologylibrary.org/cgi/reprint/106/10/3343>.
  53. *Id.*
  54. *Id.*
  55. *Id.*
  56. Sahr, *supra* note 15, at 14.
  57. Bennett et al., *supra* note 50, at 1404. Red cell aplasia occurs when the body's immune system no longer recognizes the native erythropoietin and develops an immune response the body's own blood cells, causing the patient's anemic condition to worsen as the patient's body begins to attack its own cells. See *id.*
  58. Bennett et al., *supra* note 50, at 1405.
  59. Sahr, *supra* note 15, at 15.
  60. Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 563 (2008).
  61. *Id.* at 563-64.

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62. *Id.* at 565.
63. Gitter, *supra* note 60, at 565.
64. *Id.* at 565–66.
65. *Id.* at 566.
66. *Id.* at 567.
67. *Id.* at 566.
68. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat 1585 (codified as amended in scattered sections of 15, 21, 35 and 42 U.S.C.).
69. 733 F.2d 858 (Fed. Cir. 1984).
70. *Roche Products, Inc*, 733 F.2d at 863.
71. Arie M. Michelsohn, “Follow-On” Biologics, *What Will It Take?*, A.B.A. SCITECH LAW., Fall 2008, at 4, 6.
72. Fed. Trade Comm’n, *supra* note 2.
73. *Id.*
74. *Id.* at 4.
75. Sahr, *supra* note 15, at 20–23.
76. Gitter, *supra* note 60, at 568–69.
77. *Id.* at 570.
78. Gitter, *supra* note 60, at 573.
79. 42 U.S.C. § 262 (2009); *see also* 21 C.F.R. §§ 601.20-25 (2009).
80. Kaldre, *supra* note 3, at 17.
81. Gitter, *supra* note 60, at 575–76.
82. Kaldre, *supra* note 3, at 20.
83. Bryan A. Liang, *Generic Safety Risks*, THE AM. SPECTATOR (July 25, 2007), <http://spectator.org/archives/2007/07/25/generic-safety-risks>.
84. Kaldre, *supra* note 3, at 21.
85. *Id.*
86. *Id.*
87. *Id.*
88. *See* John A. Tessensohn & Shusaku Yamamoto, *Japanese Biotech Patenting Strategies in the Era of Follow-On Biologics*, 28 BIOTECH L. REP. 483, 484, 490 (2009).
89. Kaldre, *supra* note 3, at 24.
90. Congressman Henry A. Waxman, Remarks at Biosimilars 2007 Conference (Sept. 24, 2007), *available at* <http://www.biosimilarstoday.com/Waxman.pdf>.
91. Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. (2009).
92. Pathway for Biosimilars Act, H.R. 1548, 111th Cong. (2009).
93. This is an arguable assertion, as most agree that the Hatch-Waxman Act has been successful in increasing the entry of generic drugs into the market. Prices for chemical drugs dropped as a result of the Act, and most states have encouraged health plans to substitute or require generic drugs. The presence of generic drugs has saved consumers billions of dollars, due to the fact that prices for drugs register a drop of 5% to 25% with the entry of the first generic into a market, a drop of approximately 50% for the entrance of a second generic, and by the time six or more generic drugs enter a market, the price can fall to a quarter of its original, brand price. Michael A. Carrier, *Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality*, 108 MICH L. REV. 37, 50 (2009). However, despite this, prices have recently been increasing. The rising trend may be attributable to the use of reverse payments, in which brand drugs pay generics to abandon patent challenges and delay their entrance into the market. *Id.* at 51.
94. A companion bill to Waxman’s Bill is pending in the Senate, sponsored by Senator Charles Schumer (D-NY), under the same title, was introduced on March 26, 2009. Promoting Innovation and Access to Life-Saving Medicine Act, S. 726, 111th Cong. (2009). As the bill is identical to Waxman’s Bill, this Paper will refer to Waxman’s Bill with the understanding that Schumer’s bill is included in the same analysis.

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95. Brian J. Del Buono, *Moving Toward a Biosimilars Pathway: The Lines are Drawn in Congress*, 22 BIO PHARM INT'L, July 1, 2009, at 46, 48, available at <http://biopharminternational.findpharma.com/biopharm/GMPs/Validation/Moving-Toward-a-Biosimilars-Pathway-The-Lines-are-/ArticleStandard/Article/detail/608685>.
96. *Id.*
97. *Id.*
98. Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. § 3(a)(2)(k)(11)(A) (2009).
99. Congresswoman Anna Eshoo, *Reps. Eshoo, Inslee, and Barton Introduce Pathway for Biosimilars Act*, Website of Congresswoman Anna G. Eshoo (D - CA) (March 17, 2009, 12:19 PM), available at [http://eshoo.house.gov/index.php?option=com\\_content&task=view&id=581&Itemid=79](http://eshoo.house.gov/index.php?option=com_content&task=view&id=581&Itemid=79) (quoting Rep. Eshoo's statement describing the new bill).
100. Eshoo, *supra* note 99.
101. Pathway for Biosimilars Act, H.R. 1548, 111th Cong. § 101(a)(2)(k)(7)(A), (a)(2)(k)(8)(A)(ii) (2009).
102. See Henry G. Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 2003 SCIENCE & CENTS: EXPLORING THE ECONOMICS OF BIOTECHNOLOGY 87, 93 available at <http://www.dallasfed.org/research/pubs/science/science.pdf>
103. *White House: 7 Years Enough to Shield Biotech Drugs*, REUTERS (June 25 2009), <http://www.reuters.com/article/idUSTRE55O6ZZ20090625>
104. Gitter, *supra* note 60, at 590.
105. See Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1293-94 (2006).
106. *Analytics and Follow-On Biologics: So Close and Yet So Far*, PHARMA MANUFACTURING.COM, <http://www.pharmamanufacturing.com/articles/2007/065.html> (last visited December 18, 2009).
107. *Id.*
108. Katia Boven et al., *The Increased Incidence of Pure Red Cell Aplasia with an Eprex Formulation in Uncoated Rubber Stopper Syringes*, 67 *Kidney International* 2346 (2005).
109. *Id.*
110. Gitter, *supra* note 60, at 599.
111. Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. (2009).
112. Gottlieb, *supra* note 17, at S7.
113. Gottlieb, *supra* note 17, at S5.
114. Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. § 3(a)(2)(k)(5) (2009).
115. *Id.* at § 3(a)(2)(k)(2).
116. *Id.* at § 3(a)(2)(k)(1) (emphasis added).
117. *Id.* at § 3(a)(2)(k)(2)(B).
118. Pathway for Biosimilars Act, H.R. 1548, 111th Cong. § 101(a)(2)(k)(4)(A)(i) (2009).
119. *Id.*
120. Insulin's patent was issued to the University of Toronto, and the patent has since expired. Robert D. Simoni et al., *The Discovery of Insulin: The Work of Frederick Banting and Charles Best*, 277 *J. Biological Chemistry* 31, 31 (2002).
121. *States Petition US FDA on Generic Insulin, Hormone*, REUTERS, 1 (Aug. 3, 2006), (available in LexisNexis- under "News & Business" search in "Reuters News" for article title).
122. *Id.*
123. *Id.* at 2.
124. *Id.*
125. Gitter, *supra* note 60, at 577-78.
126. *Id.* See also Sahr, *supra* note 15, at 20-23.
127. Gitter, *supra* note 60, at 578.
128. *Id.*