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## Healthy Competition

# The Case for Generic and Follow-On Biologics

*By Gregory Conko*

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### Executive Summary

Since the very first biotechnology-derived medicine was introduced in 1982, the technology has revolutionized the pharmaceutical industry. Today, more than 187 of these biopharmaceuticals have been approved in the United States, and have been prescribed to approximately 325 million patients. Biotechnology has delivered extraordinary medical advancements and has helped to treat diseases once thought intractable.

The biotechnology revolution has not come cheap, however. Many biopharmaceuticals cost thousands of dollars for a course of treatment that can last months or years. But, because the patents on many first-generation biotech medicines are slated to expire in the coming decade, there is a growing interest among patients, insurers, governments, and the generic drug industry in the production of generic biopharmaceuticals.

Some experts have speculated that the approval of generic biopharmaceuticals could save patients billions of dollars each year. However, biopharmaceuticals and conventional drugs are regulated in different ways, and the shorter approval mechanism for generic drugs does not apply to most biopharmaceuticals. Some biopharmaceuticals are regulated under the same process as conventional drugs, but most are regulated under an entirely different statute. Consequently, many groups have sought the creation of a new abbreviated regulatory pathway for generic—or what the FDA calls “follow-on”—biopharmaceuticals.

It may be possible for FDA to establish such an abbreviated approval process on its own, and the agency’s initial attempt to create such a process for generic conventional drugs may serve as a useful model. That effort was frustrated, however, by a variety of inefficiencies, so new statutory authority is probably necessary to make the approval process for follow-on biopharmaceuticals efficient and effective. Members of Congress have introduced legislation that would do just that, but there remain several practical problems that must be addressed.

Skeptics argue, for example, that the existing difference in regulatory treatment reflects the fact that biopharmaceuticals are substantially more complex and prone to contamination, which complicates the production of accurate copies. While there is some merit to these claims, the current state of biotech science has made it possible to generate safe and effective duplicates of many biopharmaceuticals. The agency has even approved one follow-on biotech drug already under the process set out for approving follow-on versions of conventional drugs. And the proposed legislation would grant FDA broad discretion to determine how much laboratory and/or human testing would be necessary for approval.

Other observers note that, because the research and development costs for biopharmaceuticals are significantly greater than for conventional drugs, and because the biotechnology industry is considerably less mature, Congress should enact special provisions—such as additional patent life or data exclusivity protections—that will help the industry remain viable. Indeed, Congress should consider certain limited incentives for innovation. However, once the patent and data exclusivity protections expire, there should be a simple and proficient method for getting approval of follow-on biopharmaceuticals.

Consumers would see tremendous benefits from an abbreviated approval process for follow-on biotech products. Many observers estimate that the introduction of follow-on biopharmaceuticals could reduce prices by 15 to 25 percent, with annual savings in the billions of dollars within a decade. In addition, the competition that follow-on approvals will generate could spur the pace of incremental improvements in biopharmaceutical quality. Thus, creating a regulatory pathway for follow-on biotech medicines would be a constructive way to advance competition in the biotechnology industry and to begin taming the rapidly increasing price of biotech medicines.



## I. Introduction

The first medical treatment produced with recombinant DNA methods, or biotechnology, was approved by the Food and Drug Administration (FDA) in 1982. Over the past 25 years, biotech medicines have been prescribed to approximately 325 million patients.<sup>1</sup> Today, more than 187 of these biopharmaceuticals have been approved in the United States, and more than 300 others are in development.<sup>2</sup> Since the 1980s, biotechnology has revolutionized the practice of medicine and the pharmaceutical industry. It has delivered extraordinary medical advancements and has helped to create medicines that treat diseases once thought intractable. Biopharmaceuticals currently are used to treat cancers, stroke, multiple sclerosis, diabetes, cystic fibrosis, and many other diseases. Many forms of cancer that were invariably fatal a decade or two ago have become treatable and even curable. Other once-fatal diseases have become manageable conditions for many sufferers thanks to biotech medicines.

The biotechnology revolution has not come cheap, however. Many biopharmaceuticals cost thousands of dollars for a course of treatment that can last months or years. Due to the industry's relative youth, most of these medicines are still protected by patents.<sup>3</sup> But, because many of the patents are slated to expire in the next decade, there is a growing interest among patients, insurers, governments, and the generic drug industry in the production of generic biopharmaceuticals. The introduction of generic conventional drugs usually leads to a sizeable drop in the price of those medicines, and some experts have speculated that the approval of generic biopharmaceuticals could save patients billions of dollars each year. Currently, though, the FDA has no formal mechanism for approving generic versions of most biotech medicines.

The 1984 Hatch-Waxman Act,<sup>4</sup> which granted authority for an abbreviated approval process for generic copies of conventional pharmaceutical drugs, was passed at a time when the biotechnology industry was in its infancy; only one biopharmaceutical product was on the market. Thus, few people even considered whether it was necessary to create a generic approval process for biotech products. Today, there is a growing need for generic biopharmaceutical approvals, but two facts complicate the process: Biopharmaceuticals are different in composition from conventional drugs, which makes them more difficult to copy. And most biopharmaceuticals are regulated under a different statute from conventional drugs.

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Biotech medicines typically are composed of large and highly complex peptide or protein molecules<sup>5</sup> that cannot be synthesized in the way conventional medicines can. Instead, they must be derived from living organisms, which gives rise to unique problems in the development and manufacture of biotech products. Consequently, most biopharmaceuticals are regulated under the Public Health Services Act,<sup>6</sup> not under the Federal Food, Drug and Cosmetics Act,<sup>7</sup> which governs conventional medicines. Hatch-Waxman applies only to the Food, Drug and Cosmetics Act, so many observers believe that FDA does not have legal authority to approve generic versions of most biopharmaceuticals.

The question of how, or even whether, generic biopharmaceuticals should be approved has become a major policy dispute. Many brand-name, or “innovator,” biotechnology companies and the Biotechnology Industry Organization (BIO), the industry’s main trade association, insist that biotech medicines are too complex and too prone to unexpected variations for generic companies to duplicate accurately.<sup>8</sup> They insist that only a full complement of clinical trials, in thousands of human patients over several years, will be adequate to demonstrate safety and efficacy. These skeptics also argue that FDA cannot ensure the “sameness” of generic biotech medicines without referring to legally protected, confidential business information contained in the innovator product’s approval application.

Within the last decade, however, scientific advances in protein characterization and purification have made it possible for generic manufacturers to make, and for FDA to approve, biopharmaceutical copies with little clinical testing needed to ensure safety and efficacy.<sup>9</sup> Indeed, the Food and Drug Administration has implicitly recognized that this is the case—at least for certain classes of biotech medicines. A 1996 FDA guidance document allows manufacturers to make significant production changes without seeking re-approval, and FDA has already approved a small number of biopharmaceutical copies after an abbreviated review process. The European Union has also adopted a regulatory framework for approving copies of biotech medicines. Thus, current experience shows that it is technically feasible to duplicate many biopharmaceuticals without sacrificing safety or efficacy.

Since 2003, the FDA has been investigating the feasibility of establishing a formal abbreviated approval process for generic—or what the agency calls “follow-on”—biotech medicines. Nevertheless, the agency has suggested that it may not have statutory authority to approve follow-on versions of many biopharmaceuticals. It has therefore been

reluctant to implement a regulatory pathway for follow-on products, despite repeated promises to do so. However, in September 2006, Sens. Charles Schumer (D-N.Y.) and Hillary Clinton (D-N.Y.), and Rep. Henry Waxman (D-Calif.) introduced bills to create a regulatory pathway for generic biopharmaceutical approvals,<sup>10</sup> and the legislation was reintroduced in both houses of Congress in February 2007.<sup>11</sup> Whether done administratively or through new statutory authorization, creating a regulatory pathway for follow-on biopharmaceuticals would be a constructive way to advance competition in the biotechnology industry and to begin taming the rapidly increasing price of biotech medicines.

## **II. Background: The Difference between Drugs and Biologics**

Historically, medicines have been broadly categorized in two different classes: “drugs” and “biological products.” Conventional pharmaceutical drugs are composed of relatively small and simple molecules that can be synthesized easily—once the chemical formula is known—using only elementary chemistry concepts. Most of the products we think of as pharmaceuticals, from aspirin to Zoloft, are classified as drugs. By their very nature, these relatively small molecules can be synthesized by nearly any expert, in almost any laboratory, with tools that can reliably produce large amounts of identical molecules, precisely guaranteeing the identity and purity of every batch.<sup>12</sup>

Biological products, on the other hand, are composed of much larger and more complex molecules that, historically, have been too intricate to synthesize. The class includes, among other things, such products as vaccines, blood products, antitoxins, and therapeutic proteins and peptides. They typically must be produced by living organisms such as bacteria, viruses, yeasts, plants, or animals, and then purified into isolated products. For example, many vaccines are simply weakened, yet live viruses.<sup>13</sup> And, until bioengineered alternatives became available in the 1980s, the insulin used to treat diabetics was purified from cow or pig pancreases,<sup>14</sup> and human growth hormone was extracted from the pituitary glands of human cadavers.<sup>15</sup>

While most biological products are not produced using recombinant DNA technology—colloquially referred to as biotechnology—essentially all biotech medicines fit into the broad category of biologicals. To make a biotech medicine, a gene comprising the cellular blueprint for the creation of a useful protein is spliced into

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the DNA of another organism. The host organism's cellular machinery is used to produce that protein, which is then purified and administered as a medicine.<sup>16</sup> So, instead of extracting porcine insulin from a pig pancreas, biotech scientists can splice the gene responsible for making human insulin into a harmless microbe and use that to produce real human insulin that is generally safer and more pure than the product it replaced.

However, because they are derived from living organisms, biological products—whether biotech-derived or “conventional”—are often difficult to purify and usually contain mixtures of both active and inactive components, both of which have the potential to affect the product's safety or efficacy. For example, a large outbreak of tetanus in 1901 was attributed to impurities in a smallpox vaccine.<sup>17</sup> In response, Congress passed the Biologics Act of 1902, which became the first national regulatory scheme for any pharmaceutical product.<sup>18</sup> The Biologics Act granted authority to the Hygienic Laboratory, predecessor of today's National Institutes of Health (NIH), to regulate the manufacturing and labeling of biologics, which the Act defined as any “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, or blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”<sup>19</sup>

Not every component of a biological product can be easily identified or measured. And, even with today's most sophisticated production technologies, each batch of many biopharmaceuticals is composed of proteins that exhibit slight differences in structure.<sup>20</sup> Consequently, biologics regulations insist on specific manufacturing controls that are designed to ensure that the end product is safe, pure, potent, and effective.<sup>21</sup> And, because even small changes in production can result in significant alterations in purity, potency, or efficacy, the manufacturer is required to notify FDA of any change in the production process, quality controls, manufacturing equipment or facilities, etc., and to demonstrate, through clinical or non-clinical tests, that the changes have not adversely affected the quality of the biological product.<sup>22</sup> Consequently, biologics regulation has historically been directed toward controlling the quality of the manufacturing “process”—including the facility in which the product was made and the inputs used—because many experts have long believed that even the slightest alteration in manufacturing could change a beneficial product into a worthless or dangerous one.<sup>23</sup>

Because the end product relies so much on idiosyncrasies of the manufacturing process, experts have historically believed that the process *is* the product, when it comes to the manufacture of biologics. Consequently, regulation initially took the form of an establishment license for the facility in which each product was made, though the product itself was not regulated.<sup>24</sup> It was not until passage of the Public Health Services Act (PHSA) in 1944 that biological products were subject to direct regulation, though regulation remains substantially concerned with the production process.<sup>25</sup> In 1972, Congress shifted responsibility for biologics regulation from NIH to FDA,<sup>26</sup> though authority for regulating biological products is still found in section 351 of the PHSA. Today, regulation of the product and facility are combined into one approval process, known as the Biological License Application (BLA).<sup>27</sup> To get approval for a biological product, the BLA must describe in detail the characteristics of the product, as well as specifics of the manufacturing process and the facility in which the product will be made.

In contrast, the Pure Food and Drug Act of 1906 (PFDA) provided only statutory authority for the U.S. Department of Agriculture's (USDA) Bureau of Chemistry to regulate drugs that were "adulterated" or "misbranded."<sup>28</sup> The 1938 Food, Drug and Cosmetics Act (FDCA) created the Food and Drug Administration, shifted authority for regulating drugs from USDA to the new agency, and established a requirement that manufacturers prove the safety of new drugs. To get approval for a drug, section 505 of the FDCA requires manufacturers to submit a New Drug Application (NDA).<sup>29</sup> The Act defines a "drug" as any article "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease" or "intended to affect the structure or any function of the body of man."<sup>30</sup> Although biological products clearly fall within the statutory definition of "drugs," biologics are still treated as a separate class of medicines.<sup>31</sup>

#### *A. Regulation of Biopharmaceuticals*

Generally speaking, drugs are regulated by FDA's Center for Drug Evaluation and Research (CDER or Center for Drugs) under section 505 of the FDCA, while biologics are regulated by FDA's Center for Biologics Evaluation and Research (CBER or Center for Biologics) under section 351 of the PHSA. Complicating matters even further, in 1941, Congress passed the Insulin Amendments, which required FDA to regulate insulin

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as a drug under section 505 of the FDCA,<sup>32</sup> even though insulin would fit more neatly into the category of biologics. From that point forward, some biologics would be regulated under the Food, Drug and Cosmetics Act and others under the Public Health Services Act, a quirk of history that has important ramifications for biotechnology regulation today.

As noted above, essentially all biotech medicines—or biopharmaceuticals—are technically biological products. A small number of biopharmaceuticals, however, have been regulated and approved as drugs under section 505 of the FDCA, as a direct, though unintended, result of Congress’s passage of the Insulin Amendments. Their enactment shifted authority over insulin and a small number of other protein- and peptide-based therapeutics, such as growth hormones, to the Center for Drugs (then called the Bureau of Drugs). And, once similar protein and peptide products began to be developed with biotechnology, they too were regulated as drugs by CDER.<sup>33</sup>

In 1981, FDA re-apportioned protein-based biotech products between CDER and CBER, with insulin, human growth hormone, and a handful of other comparatively small and “well-characterized” proteins being classified as drugs, and all others classified as biologics.<sup>34</sup> Nevertheless, while protein products such as insulin were regulated as drugs, the fear of difficult-to-detect contaminants remained, and the approval process for those biopharmaceuticals continues to include a certification of the manufacturing process.<sup>35</sup>

Today, however, the comparative precision of, and the highly sophisticated tools used in, biotechnology has made it much easier for manufacturers to characterize both the active and inactive components of biological products, and it has given them much greater control over the production process. As a result, the FDA approval process for manufacturing changes in biologics—but especially biotech biologics—has evolved to allow for greater and greater flexibility.<sup>36</sup> In 1996, the Center for Drugs and Center for Biologics jointly issued a guidance document that spells out how biologics producers can go about making “manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy.”<sup>37</sup>

Manufacturers might, for example, change the fermentation or purification processes to improve product quality or yield, which a generation earlier might have necessitated new human testing to ensure the product was therapeutically unchanged. However, FDA noted at that time that improvements in test methods and product characterization

have allowed manufacturers to “establish sensitive and validated assays for characterizing the product and the biological activity ... [such that it] can provide the basis for FDA to assess product comparability without the necessity of repeating clinical trials.”<sup>38</sup> So long as the manufacturer’s testing can, in FDA’s judgment, demonstrate that the pre- and post-change products are “comparable” in safety, identity, purity, and potency, the agency will allow for increasingly substantial changes to be made without extensive human testing.<sup>39</sup>

Not all manufacturing changes may be made with so little agency oversight, of course. Significant changes in the production or purification of biologics products—such as a re-creation of the cell line—still often require at least limited clinical trials in which the manufacturer must demonstrate comparable safety and efficacy. Nevertheless, the new flexibility promoted by the 1996 guidance was based on a recognition that use of modern biotechnology in the production of biological products makes them much less prone to contamination and makes it far easier for manufacturers to confirm protein identity and purity. Indeed, as molecular characterization and purification become increasingly more precise, modern biotechnology may one day fully bridge the gap between conventional drugs and traditional biologics.

### *B. The Paper-NDA and Hatch-Waxman*

The regulation of small-molecule drugs changed dramatically in 1962, upon passage of the Kefauver-Harris Drug Amendments<sup>40</sup> to the FDCA. Enacted in the wake of the European thalidomide tragedy, the 1962 Drug Amendments substantially expanded the requirements for approving new medicines. Not only would manufacturers have to demonstrate that new drugs were *safe*, they would also have to conduct, in most cases, at least two “well-controlled clinical investigations” demonstrating that the drugs were *effective* to a high degree of statistical significance.<sup>41</sup> Manufacturers now must typically conduct three phases of graduated clinical trials (Phase I and Phase II to demonstrate safety, and Phase III to demonstrate efficacy) on thousands of human subjects.

These new requirements changed the very nature of the drug industry by adding substantially to the length of time it takes to develop, test, and seek approval for new drugs, and by making it considerably more expensive to do so.<sup>42</sup> This had two significant effects. First, because of the longer testing and approval times, a sizeable portion of each drug’s patent life was exhausted before the drug ever reached the market. Second,

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generic manufacturers would have to go through the same testing and approval process as brand-name “innovator” drug manufacturers. Prior to 1962, most generic manufacturers just put their products on the market with no FDA review. Their products were copies of already approved products, not “new drugs,” so they were not technically subject to the 1938 Act’s review requirements. The Kefauver-Harris Amendments changed that, effectively destroying the very possibility of a broadly competitive generic drugs industry because few manufacturers were willing to expend the resources of bringing generic drugs, which have lower profit margins than brand-name drugs, to market.<sup>43</sup>

FDA’s response to the dearth of new generic drugs was to create, administratively rather than through a grant of specific statutory authority, a shortened drug application process. FDA has considerable discretion under the FDCA to determine what kind of evidence is necessary to satisfy the requirements of section 505’s safety and efficacy standard. Consequently, in 1978 the agency drafted an internal process document<sup>44</sup> that allowed a generic manufacturer to apply for approval based, not on its own clinical studies, but almost entirely on safety and efficacy studies conducted by others that were published in the peer-reviewed scientific literature.<sup>45</sup> To get approval, a generic manufacturer merely needed to prove through laboratory testing that its product was chemically equivalent to the innovator, or “reference,” drug and had to supply sufficient published information—rather than raw data generated from its own clinical studies—to demonstrate safety and efficacy. The process became known as the “paper NDA.”<sup>46</sup>

By 1984, 15 generic drugs had been approved under this new process.<sup>47</sup> Unfortunately, the paper NDA had several shortcomings. FDA estimated that, of the innovator drugs approved since the Kefauver-Harris Amendments, published scientific information sufficient to support a paper NDA existed for only 15 percent of them.<sup>48</sup> Consequently, generic versions of many innovator drugs simply could not be approved using a paper NDA due to the lack of sufficient published scientific reports. In addition, brand-name companies claimed that FDA was improperly using proprietary data contained within innovator NDAs to evaluate paper NDAs. Several brand-name manufacturers filed lawsuits, but in each case, FDA’s use of the paper NDA was upheld by the courts.<sup>49</sup> However, the prospect of extensive litigation and the dearth of relevant published data made many generic manufacturers hesitant to make expansive use of the paper NDA process.

To break this logjam, in 1984 Congress passed the Hatch-Waxman Act, which codified the paper NDA process by adding the new section 505(b)(2) to the FDCA. The Act also added section 505(j), which grants FDA specific authority to approve generic drugs that rely solely on the proof of safety and efficacy in the reference drugs' NDAs. In exchange for the brand-name manufacturers' support, the Act further provided for certain limited extensions to the patent life of innovator drugs.<sup>50</sup>

Because drug patents usually must be filed many years before the drugs are approved, a provision in the Hatch-Waxman Act allowed manufacturers of innovator drugs to restore several years of patent life lost while the drugs were being tested and while FDA reviewed the NDAs. The Act also ensures a five-year "data exclusivity" period, during which the agency may not, without the innovator's consent, refer to data in the innovator's NDA when considering an application from a generic competitor seeking approval for an equivalent product. The goal was to protect the incentives for pharmaceutical companies to invest in continuous innovation, while ensuring that patent terms would eventually expire, thereby permitting generic competition.<sup>51</sup>

The Act proved to be highly successful in promoting the introduction of generic drugs. Today, more than one billion generic drug prescriptions are filled every year, and generics account for roughly half the pharmaceutical market in the United States.<sup>52</sup> A 1998 study by the Congressional Budget Office concluded that generic drugs save U.S. consumers between \$8 billion and \$10 billion every year.<sup>53</sup> And, whereas in 1983 only one-third of the top-selling drugs approved after the 1962 Drug Amendments faced competition from a generic version, by the late 1990s, nearly all did.<sup>54</sup>

### *C. Structure of the Hatch-Waxman Act*

The Hatch-Waxman Act's primary generic drug pathway is contained in its section 505(j), which requires generic manufacturers to submit an abbreviated new drug application (ANDA) showing that the generic drug contains the "same" active ingredient as the reference product; is "bioequivalent" to the reference drug; and has the same strength, dosage, form, labeling, and conditions of use as the reference drug.<sup>55</sup> Hatch-Waxman explicitly authorizes FDA to approve ANDAs based solely on the fact that the innovator drug has already been shown to be safe and effective. And, once approved under 505(j), most of these generic drugs

are considered to be therapeutically equivalent to the innovator drugs and receive the agency's "A" rating of equivalence, which means they can generally be interchanged freely with the reference drug.<sup>56</sup>

In the alternative pathway created by section 505(b)(2), the approval process is abbreviated, but the manufacturer still must submit some amount of clinical or non-clinical data—determined by the agency at its discretion—that demonstrates the new product's safety and efficacy. As with the paper NDA, this can take the form of previously published research in the place of, or in addition to, studies actually conducted by the manufacturer. Such information may also include reference to a previously approved product, but the chemical structure of the applicant drug need not be identical to the reference product. The section 505(b)(2) pathway is therefore typically used to approve a change in dosage, form, strength, or route of administration, a subtle change in formulation or active ingredient (such as a different salt, ester, or other compound of the original molecule), or a new combination of previously-approved drugs to be used together.<sup>57</sup> Consequently, products approved under section 505(b)(2) may be prescribed as alternatives to the reference drugs, but, because "sameness" and "bioequivalence" have not been demonstrated, they are not viewed as being freely interchangeable.<sup>58</sup> They are therefore not referred to as "generics," but only as "comparable" or "follow-on" drugs.<sup>59</sup>

Another important distinction between the 505(j) true generics pathway and the 505(b)(2) pathway for comparable products is that reliance on an already approved drug's safety and efficacy is appropriate only regarding those characteristics that the new drug shares with the approved reference drug. "For any modification or change from the reference drug, an applicant must submit appropriate data establishing that the drug with the modification or change satisfies the statutory requirement of safety and efficacy."<sup>60</sup> NDAs submitted under section 505(b)(2), therefore generally rely only in part on the approval of a reference drug, so they must contain some amount of previously published or original clinical or non-clinical research demonstrating approvability. Importantly, though, section 505(b)(2) does alleviate the need for manufacturers to conduct scientifically unnecessary research that wastes resources and runs the ethical risk of some patients in clinical trials receiving placebo instead of a therapeutically useful treatment.

The Food and Drug Administration has approved a number of follow-on drug applications under section 505(b)(2),<sup>61</sup> but the process has not been without controversy. Because the statutory language is not clear on the point, some innovator drug manufacturers have argued that 505(b)(2) applicants may only rely on information in the innovator's NDA that is already in the public domain, not on information that is still a protected trade secret.<sup>62</sup> FDA and some observers maintain that the agency does have statutory authority to rely on otherwise protected data in the reference product's NDA, so long as the data is not made public.<sup>63</sup> These concerns have arisen again in the generic biopharmaceutical debate and will be discussed below.

### **III. Biopharmaceuticals and the Follow-On Process**

Today, annual revenue for the biotechnology industry exceeds \$39 billion per year,<sup>64</sup> and it is expected to reach \$90 billion by 2010.<sup>65</sup> Many biotech medicines cost patients several thousand dollars each year—some more than \$50,000 annually per patient.<sup>66</sup> Dozens of top-selling biopharmaceuticals have recently come off-patent or will soon reach the end of their patent lives, however, and many consumers, health insurers, and health care providers are eagerly awaiting the day when generic versions of these medicines will be available.

Because the thought of accurately reproduced biological products was merely a theoretical possibility when the Hatch-Waxman bill was being debated in the early 1980s, that legislation makes no mention of an abbreviated approval process for items regulated under the Public Health Services Act—only those regulated as drugs under the Food, Drug and Cosmetics Act. Critics of generic biotech products have argued that, consequently, FDA has no statutory authority to approve biotech medicines with less than a full complement of original clinical trial data.<sup>67</sup> These critics also insist that, because biotech products (even those that are regulated as drugs) have most of the same production idiosyncrasies as conventional biologics, manufacturers of generic or follow-on biopharmaceuticals would be unable to replicate both the therapeutic protein *and* the precise manufacturing process used in making innovator products. Furthermore, because replicating the production process and proving comparability or bioequivalence would require referencing information available only in the innovator product's BLA or NDA,

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many in the biotechnology industry insist that doing so would unlawfully infringe on protected trade secrets.

The biotech industry has raised important scientific questions that will be addressed below. But, while there are technical obstacles to implementing a generic biopharmaceutical approval pathway, it is not clear that FDA completely lacks statutory authority to approve generic or follow-on biotech products using some form of abbreviated application process. The small number of biopharmaceuticals approved as “drugs,” rather than “biologics,” already are subject to the Hatch-Waxman approval pathways, and those approved under the Public Health Services Act likely could be approved using a pathway analogous to the paper NDA process used prior to Hatch-Waxman for the approval of comparable follow-on drugs.

Biotech products approved as drugs under the Food, Drug and Cosmetics Act clearly fall within the authority of the Hatch-Waxman Act, and copies may be approved under section 505(b)(2) for follow-on products or section 505(j) for true generics. A 1999 FDA draft guidance document specifically identifies biotech, or “recombinant,” products as falling within the class of products that could be approved pursuant to section 505(b)(2).<sup>68</sup> A final version of that document has never been published, but FDA has already approved several biotech protein products under section 505(b)(2), including GlucaGen in 1998,<sup>69</sup> Follistim in 2002,<sup>70</sup> Hylenex and Fortical in 2005,<sup>71</sup> and Omnitrope in 2006.<sup>72</sup> Of these, all but Omnitrope were the first biotech, or recombinant, versions of natural hormones that had been used therapeutically in the United States for many years. Skeptics argue that they are therefore not truly “follow-on” products, but innovator products. Nevertheless, these abbreviated approvals under 505(b)(2) indicate that FDA has begun to reconsider the “process is product” philosophy that has governed biologics regulation since 1902—at least so far as small and relatively well-characterized protein products are concerned. In any event, for some classes of biological products, FDA has clearly acknowledged that it not only has the legal authority to approve follow-ons under the FDCA, but also that advances in protein characterization and purification make it technically feasible to compare the safety and purity of proteins arising from two different manufacturing processes.<sup>73</sup>

Perhaps more importantly, FDA has always had a substantial amount of discretion to determine how much data, and in what form, it would require manufacturers to submit in support of new product applications. Indeed, while explicit statutory authority was eventually

granted by the Hatch-Waxman Act, several federal courts did uphold FDA's paper NDA process. Consequently, there seems to be no statutory barrier preventing FDA from implementing an abbreviated approval process for follow-on biologics under the Public Health Services Act where the second manufacturer can demonstrate to FDA's satisfaction that the follow-on product is "comparable" to the innovator product in safety, identity, purity, and potency. However, there is a lingering statutory question regarding how much the FDA can rely upon the reference drug's prior approval in determining the comparability of such a follow-on.

#### *A. Trade Secrets and FDA's 1999 Guidance Document*

The 1999 FDA draft guidance document was quite controversial, as it specifically endorsed allowing applications for follow-on biotech products under the 505(b)(2) approval pathway. But, more importantly, the draft guidance reiterated FDA's view that the Hatch-Waxman Act permits section 505(b)(2) follow-on applications to "rely on the agency's findings of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions of section 505(j)."<sup>74</sup>

The innovator pharmaceutical industry criticized the guidance document as agency overreach, and it argued that allowing 505(b)(2) follow-on approvals, even for biotech products first approved as drugs, would necessarily have to involve a use of confidential business information contained within the reference product's NDA, which is forbidden by the Trade Secrets Act. Because drugs approved under section 505(b)(2) are generally not identical to their reference drugs (else they could be approved under section 505(j)), many innovator companies fear that FDA would actually have to look beyond the mere finding that the innovator drug is safe and effective and delve into the relevant underlying data in the innovator NDA to identify areas of similarity and difference. Thus, they argue that analytical methods are currently insufficient to make a precise comparison of an innovator and follow-on biological product without consulting data related to the production process that is contained in the reference product's NDA.<sup>75</sup>

In 2001, brand name companies Pfizer and Pharmacia jointly submitted a citizen petition asking FDA to forbid generic manufacturers from submitting applications that required FDA to compare "non-public proprietary information in an innovator's New Drug Application" to

data in the follow-on application.<sup>76</sup> Allowing FDA to do so, they argued, would not only violate the Trade Secrets Act, but would also constitute a “taking” that would entitle the innovator firm to compensation under the Fifth Amendment to the U.S. Constitution.<sup>77</sup> Several other brand name companies, including Abbott Labs, Amgen, and Bristol-Myers Squibb, followed suit. And, in April 2003, the Biotechnology Industry Organization (BIO) submitted a citizen petition to FDA urging the agency to (1) withdraw the 1999 draft guidance, (2) “conduct a meaningful public participation process on the agency’s policies regarding “follow-on approval” of therapeutic proteins,” and (3) “refrain from preparing, publishing, circulating or issuing any new guidance for industry” related to approval of therapeutic proteins under 505(b)(2) or FDA’s earlier “paper NDA” policy.<sup>78</sup> According to BIO, approving follow-on biotech products without referring to the manufacturing data contained in an innovator’s NDA is not feasible because “structural heterogeneity, the critical effects of the manufacturing process, [and] immunogenicity concerns” all make true replication of a protein difficult or impossible.<sup>79</sup>

In its October 2003 reply,<sup>80</sup> FDA made clear that it did not view anything in the 1999 guidance document as violating the Trade Secrets Act or to constitute a taking. As early as 1938, FDA had held that unpublished data included in an NDA (or BLA) were confidential trade secrets that could not be disclosed by the agency or used by another manufacturer to support approval for other products without the innovator company’s permission.<sup>81</sup> But the Hatch-Waxman Act explicitly changed that. Section 505(b)(2) specifically authorizes FDA to approve NDAs that include research “not conducted by or for the applicant, *and for which the applicant has not obtained a right of reference or use.*”<sup>82</sup> [Emphasis added.] This passage seems clearly to permit 505(b)(2) applicants to rely on data that is included in the reference drug’s NDA, even though the follow-on applicant does not otherwise have a legal right to use or rely upon that data.

More importantly, only FDA personnel actually examine the innovator’s data. Agency officials may not disclose proprietary data, but agency personnel are free to rely on information contained in NDAs (or BLAs) when reviewing the safety and efficacy of follow-on products. To the extent that there are clinically relevant differences between the innovator and follow-on products, the 505(b)(2) applicant may only rely on FDA’s finding of safety and efficacy for those aspects in which the two are the same. FDA must, nevertheless, be able to rely upon the innovator’s

NDA to identify the differences, so it can require the 505(b)(2) applicant to supply sufficient additional data with its application.

As FDA points out in its 2003 reply to BIO’s petition, the purpose of including section 505(b)(2) in the Hatch-Waxman Act in the first place was to “permit the pharmaceutical industry to rely to the greatest extent possible under the law on what is already known about a drug.”<sup>83</sup> In addition, Hatch-Waxman’s legislative history supports the view that section 505(b)(2) was intended to go beyond the paper NDA, in which applicants relied solely on published studies, and to permit some degree of reliance on data in the innovator’s NDA.<sup>84</sup> Requiring 505(b)(2) applicants to reproduce scientific studies that have already been produced by the innovator applicant “would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health.”<sup>85</sup> Consequently, interpreting section 505(b)(2) in such a way as to forbid any reliance on otherwise confidential data within an reference drug’s NDA would frustrate the very purpose of the Hatch-Waxman Act.

Nor would FDA reliance on the data be considered a compensable taking under relevant Supreme Court case law. Although the Trade Secrets Act makes it unlawful for government agencies to disclose trade secrets contained in a manufacturer’s product approval application, those provisions do not forbid government employees from relying upon an applicant’s otherwise protected data when approving later products.<sup>86</sup> In one seminal case,<sup>87</sup> the Supreme Court held that, even where protected trade secrets are submitted to a federal agency for the purpose of a regulatory safety approval, the applicant could not have any reasonable investment-backed expectation that the agency would not later use that information in a way that benefited a subsequent applicant because, “[i]n an industry that has long been the focus of great public concern and significant government regulation, the possibility was substantial that the Federal Government ... would find disclosure to be in the public interest.”<sup>88</sup> According to the Court, “statutory silence in a heavily regulated industry ... places applicants on notice that they cannot form reasonable investment-backed expectations that submitted data will not be used by the agency in the future.”<sup>89</sup>

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*FDA surprised many observers by noting that nothing in Hatch-Waxman “precludes approval of [biotech product] applications ... under section 505(j) of the Act,” which addresses true generics, “as long as the current state of science allows the evaluation necessary to support approval.”*

#### **IV. FDA Approval for Follow-On Biotech Drugs**

FDA’s approvals under section 505(b)(2) of protein products such as GlucaGen and Follistim were greeted with little fanfare—perhaps because they were only the first recombinant versions of natural proteins, rather than copies of previously approved biopharmaceuticals. However, another product, Sandoz, Inc.’s Omnitrope—a follow-on version of Pfizer’s human growth hormone Gentropin—proved to be quite controversial. Generics maker Sandoz, a subsidiary of the brand-name pharmaceutical company Novartis, submitted a 505(b)(2) application for Omnitrope in July 2003.<sup>90</sup> The application was based, in part, on FDA’s prior approval of Gentropin, but also on original pre-clinical and clinical toxicology data, comparability data, and the results of Phase III clinical studies conducted by Sandoz.<sup>91</sup>

Pfizer responded by submitting a citizen petition specifically requesting that FDA not grant approval for Omnitrope because doing so would violate the Trade Secrets Act.<sup>92</sup> Pfizer also insisted that, even if FDA did use the protected information, FDA still would “not be able to confirm the batch-to-batch reproducibility, stability, level of adverse events, dosing and overall safety and effectiveness” of Omnitrope without requiring a complete set of clinical trials.<sup>93</sup> In August 2004, FDA sent a letter to Sandoz acknowledging that the agency had completed its review of Omnitrope, but that, due to the application’s “nature and complexity,” the agency would defer a decision until it had an opportunity to collect additional scientific information.<sup>94</sup>

In the interim, FDA initiated a series of public scientific meetings at which experts from both brand-name companies and generic manufacturers, as well as independent scientists, were invited to make presentations on the state of the art in biotechnology and protein chemistry. Meetings were held in September 2004, February 2005, and December 2005. After the February 2005 workshop, CDER head Janet Woodcock announced that FDA would soon release a draft guidance document outlining what the agency considered to be sufficient data standards for follow-on protein product applications.<sup>95</sup> By May of that year, however, *Business Week* reported that follow-on biotech products were in a “regulatory limbo—and likely to stay there.”<sup>96</sup> And, in October 2005, FDA Deputy Commissioner Scott Gottlieb announced that the agency “does not plan to release any documents concerning follow-on biologics regulation in the near future.”<sup>97</sup> Rather than raising a scientific concern,

however, Gottlieb said that, although the agency “probably” could approve follow-on biologics through the section 505(b)(2) pathway, the question “remains very much open both from a legal and regulatory standpoint.”<sup>98</sup> Gottlieb also indicated that FDA did not believe it had authority to approve follow-on products regulated under the PHSA. At least one of these questions would be resolved the following year, however.

After Omnitrope maker Sandoz received FDA’s August 2004 letter informing the company that the agency would defer approval, Sandoz took the justified, but unusual step of challenging that decision in court. Most manufacturers are loath to challenge an agency, such as FDA, that has so much discretionary power over product approvals, even when agency decisions appear arbitrary or capricious. But, in an action filed in September 2005, Sandoz charged the agency with violating a statutory obligation to act on new product applications within 180 days of submission.<sup>99</sup> FDA argued that the 180-day deadline was merely a target: “aspirational rather than mandatory.”<sup>100</sup> The court disagreed, and in April 2006, it ordered FDA to either approve or reject the Omnitrope NDA. A little over one month later, FDA approved Omnitrope under section 505(b)(2).

The same day, FDA explained its rationale for approving Omnitrope in a formal reply to the 2003 BIO petition and the 2004 Pfizer petition.<sup>101</sup> FDA wrote that the characteristics that made Omnitrope eligible for the 505(b)(2) pathway include: a single active ingredient, a well-known mechanism of action, and the ability to “extensively and adequately” characterize the protein.<sup>102</sup> And FDA hinted that future products meeting these and the other listed criteria would also qualify. In responding to BIO’s assertion that it is not technically feasible to prove that two biotech proteins produced by different manufacturers were the “same,” FDA dispensed with the “process is the product” mantra and concluded that follow-on manufacturers need not prove “sameness;” they need only show that any differences are not clinically meaningful.<sup>103</sup>

FDA surprised many observers by also noting that nothing in Hatch-Waxman “precludes approval of [biotech product] applications ... under section 505(j) of the Act,” which addresses true generics, “as long as the current state of science allows the evaluation necessary to support approval.”<sup>104</sup> Thus, it signaled its view that statutory authority does exist for approving true generic biotech products, so long as they are copies of products previously approved under the FDCA. The agency suggested

that actually demonstrating “sameness,” as that section requires, was most likely beyond current scientific capabilities, however. But that opinion leaves open the possibility that true generic biopharmaceutical approvals will be a reality when protein characterization techniques are sufficient to support them.

In defending the Omnitrope approval, FDA also drew a distinction between FDCA section 505(b)(2) and the PHSa, and noted that the former “explicitly permits applicants to rely for approval on data from investigations ‘not conducted by or for the applicant.’”<sup>105</sup> By omission, then, FDA implied that the agency believes it does not currently have statutory authority to refer to data in an innovator’s Biologics License Application when reviewing a follow-on product regulated under the Public Health Services Act. Though FDA did not clearly indicate that it could never approve biological products with an abbreviated BLA process, the inability to rely upon data in a reference product’s BLA would severely limit FDA’s ability to approve follow-on biologics under current statutory authority. Just as FDA experimented with a “paper NDA” process in the late 1970s, there appears to be no *statutory* reason why it could not implement a “paper BLA” now. But, due to current technical limitations, new statutory authority may well be needed if there is to be a meaningful follow-on biologics approval pathway.

Just as threats of litigation and the existence of few useable scientific studies in the peer reviewed literature ultimately doomed FDA’s paper NDA, so too does a paper BLA appear to be impractical. That is why so many observers have insisted that new statutory authority is necessary. In any event, by the summer of 2006, it seemed clear that FDA would not move forward with a proposal for approving follow-on products. That put the onus squarely on Congress to determine whether it would grant FDA explicit authority to approve follow-on biologics. In September 2006, Sens. Charles Schumer (D-N.Y.) and Hillary Clinton (D-N.Y.), and Rep. Henry Waxman (D-Calif.) introduced legislation to do just that,<sup>106</sup> and the bills were reintroduced in both houses of Congress in February 2007.<sup>107</sup> Democratic Party leaders in the House and Senate have indicated that follow-on biotech medicines authorization will be a priority.<sup>108</sup>

## V. Can Follow-On Biologics Be Approved Safely?

While it appears that Congress may now have the will to give FDA statutory authority to approve follow-on biologics with an abbreviated review mechanism, one question remains: Given that safety is a legitimate concern, *should* FDA have that authority? The manufacturing process for biological products, including biotech biologicals, is highly complex and involves a “production cascade” in which the cells used to generate the end product first produce amino acids that are then joined together to form a protein, which is often then altered by rearrangements and the addition of other molecules. Production is complicated further by the possibility that clinically significant changes may be made in the purification, analysis, or packaging of the biological product.<sup>109</sup> Though some critics have vastly overstated the difficulty of replicating relatively small and well-characterized protein products in a new manufacturing process, it is true that biopharmaceuticals are more difficult to reproduce than simple, small-molecule drugs. Some classes of biological products cannot even be completely characterized—let alone accurately duplicated—using even the most sophisticated current technology.<sup>110</sup>

Critics of follow-on biologics often illustrate the importance of these concerns by pointing to one instance in which very serious immune reactions were associated with a manufacturing change to a version of the biotech hormone erythropoietin (Epo) produced by an innovator firm.<sup>111</sup> Patients with chronic renal failure often develop anemia due to a decline in the body’s production of natural erythropoietin, and Epo is commonly prescribed to treat the anemia. At least four pharmaceutical companies sell different versions of biotech Epo in the U.S.—though each was approved individually as an “innovator” drug, not as a follow-on product.<sup>112</sup> One known but rare side-effect of long-term Epo use is an immunological response called pure red cell aplasia, in which a small number of patients produce antibodies that attack and effectively neutralize both biotech and natural erythropoietin. After a 1998 manufacturing change, patients taking Johnson & Johnson’s Eprex brand Epo began suffering an unusually large number of pure red cell aplasia cases.<sup>113</sup> Johnson & Johnson eventually identified the source of the problem and altered its manufacturing process to correct it.

A similar problem also occurred in the early 1980s during the clinical testing of a new human growth hormone formulation by an innovator firm.<sup>114</sup> A low-level contaminant in the product resulted in

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an immune system response that caused extreme pain at the injection site, fever, and other symptoms. But the contaminant had not been detected in either lab testing or pre-clinical animal testing. Of course, even full clinical testing of new drugs and biologics on thousands of trial participants is not always sufficient for spotting potential problems because very rare side effects may only be detected when the product is used by much larger numbers of patients.<sup>115</sup> Nevertheless, the incidents do highlight the special difficulties associated with re-producing biological products. Still, the fact that these incidents arose with innovator, not follow-on, products should give one pause before condemning out of hand the potential of follow-on biopharmaceuticals. These risks are not unique to follow-ons; they occur in all biological products.

#### *A. Safety Challenges*

Perhaps the two biggest challenges in creating safe and effective follow-on biopharmaceuticals is confirming clinical comparability and ensuring that recreated biotech medicines do not pose new immunogenicity risks. While the potential for unanticipated changes must always be considered when manufacturing biological products, state-of-the-art scientific tools and methods are far more advanced than those of only a decade ago, when Johnson & Johnson experienced problems with Epo. Today, sophisticated analytical tools make it possible to purify protein samples from genetically-engineered cells with a very high degree of confidence and precision and to verify the structure of those proteins.

The therapeutic value of a protein depends on its amino acid sequence, its exact folded structure, and the presence or absence of certain other modifications made to the protein by cellular machinery. Older technologies are fully capable of identifying the sequence of amino acids in a protein, but they are less reliable in identifying the precise structure of the folded protein molecules. Using today's most sophisticated tools, however—such as multiple-stage chromatography and mass spectrometry, combined with immunoassays—can improve the final product's overall purity. And the identity, composition, and structure of purified proteins can be verified using a number of other chemical and physical analyses, such as peptide mapping, nuclear magnetic resonance imaging, and x-ray crystallography.<sup>116</sup> While fully characterizing the largest and most complex proteins may still be beyond the reach of current technology, many of the biopharmaceuticals now on the market can be copied, and their structure and purity verified.

Special problems may arise when addressing proteins that have been subject to what are known as “post-translational” modifications. After proteins are “translated” from the novel gene by messenger RNA, certain cell types can subsequently change that protein by, for example, folding it in a new way, rearranging the amino acid sequence of the protein, or adding additional molecules to the protein. Each of these changes can have important effects on the protein’s structure and function, as well as its therapeutic value.<sup>117</sup> For example, in a process known as glycosylation, some host cell types add sugar molecules to the protein after it is generated. This can, but does not always, affect the protein’s therapeutic properties, and even small differences in the pattern of glycosylation can have significant impacts.<sup>118</sup>

Similarly, different production processes may result in very small changes in the sequence of amino acids that make up the proteins. In some cases, even a single amino acid change can make the protein ineffective or unsafe, though in many cases minor changes in amino acid sequence have no real effect.<sup>119</sup> Still, while such differences as glycosylation and amino acid alteration *may* generate clinically meaningful changes, existing technology can identify them, and FDA can use these tools to differentiate among products that should or should not qualify for abbreviated approval pathways. In any event, *in vitro* analysis and limited clinical testing can further aid scientists in understanding many proteins’ modes of action and, in turn, help compare the functional performance of a follow-on to that of its reference product.

Though all biological products have the potential to trigger immunogenicity problems—a response from the patient’s immune system that could counteract the biologic’s therapeutic effect or even harm the patient directly—the presence of these risks after a manufacturing change is often assessed without extensive clinical trials.<sup>120</sup> While not perfect, basic laboratory testing, such as bioassays and animal studies, and limited human testing are typically sufficient to spot the factors that are known to be implicated in immunogenic reactions. There is little reason to believe that most immunogenic problems cannot be resolved prior to the approval of a follow-on biologic—or, as is current practice, of an innovator’s manufacturing change—especially if the results of the reference product’s pre-clinical and clinical analyses are available to regulators for a comparison.<sup>121</sup>

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The exact folding and other structural characteristics of some of the largest and most complex proteins may still not be able to be mapped with certainty, making their follow-on approval untenable at the present time. But for relatively simple protein molecules (some of which are regulated as drugs, and others as biologics), current technology makes follow-on approval both realistic and safe. In approving Omnitrope, for example, FDA explained that the characteristics that made it eligible for the follow-on drug pathway included a single active ingredient, a well-known mechanism of action, and the ability to “extensively and adequately” characterize the protein.<sup>122</sup> The agency further explained that future products meeting these and the other listed criteria very likely would also qualify for abbreviated review. Indeed, for small proteins such as these, some experts argue that it may already be possible to demonstrate “sameness” to the degree necessary for true generic approval under the Food, Drug and Cosmetics Act’s section 505(j) or an equivalent for the Public Health Services Act.<sup>123</sup>

*B. Existing Regulatory Approaches Lead the Way*

FDA’s 1996 guidance document, as well as its approval of several biotech drugs under section 505(b)(2), indicate that, for relatively simple protein products, agency scientists are already comfortable with their ability to identify the majority of clinically significant effects inherent to manufacturing changes that will necessarily result in the production of follow-on biologics. Several other countries have already established regulatory platforms for the approval of follow-on biological products. For example, in 2005, Australia became the first country to approve Sandoz’s Omnitrope.<sup>124</sup> Likewise, the European Union has recently introduced a policy for the approval of what it calls “similar biological medicinal products,” or “biosimilars.”<sup>125</sup>

The EU’s legal framework for biosimilar products is based on the premise that existing technology makes it possible for regulatory authorities to verify the comparability of biosimilars. Approving them requires less supporting data than did the approval of the reference product, even when they do not meet all the conditions to be considered true generics.<sup>126</sup> And EU regulators have wide discretion to determine when an applicant has satisfied the statutory requirements for safety and efficacy.

In a sense, the EU's approach is equivalent to section 505(b)(2) of the Hatch-Waxman Act, in that the biosimilar applicant can rely, to some extent, on the European Medicines Agency's (EMA) prior approval of the reference product in order to meet some, though not necessarily all, of the quality, safety, and efficacy requirements. And, in both the 505(b)(2) pathway for follow-on drugs and the EU's biosimilar pathway, the determination of when the manufacturer has supplied sufficient evidence of safety and efficacy is determined by the regulatory agency. The EU's statutory framework differs from the 505(b)(2) pathway however, by also allowing producers of follow-on biological products to apply for—and to be granted where appropriate—true generic approval. EU regulators currently believe that the state of the science does not yet allow examiners to verify that a follow-on product is identical to its reference product to the degree necessary for such approvals,<sup>127</sup> but the legal process now exists and will be available when the technology reaches an appropriately advanced state.

European regulators, nevertheless, believe that they can safely approve non-generic biosimilar products with abbreviated applications, the stringency of which is determined on a product-by-product basis. Depending upon the complexity of the underlying product, a biosimilar application could require a range of support materials, from limited or no clinical trial data for very small and well-characterized proteins to nearly-complete data packages, such as might be required for an innovator product, for more complex and less familiar molecules.<sup>128</sup> While a number of biosimilar product applications have been submitted to the European Medicines Agency, only two have been approved for sale in the European Union: One of these is the Sandoz human growth hormone product Omnitrope, discussed above; the other is also a human growth hormone, called Valtropin, produced by BioPartners GmbH. A third product, Alpheon, an interferon produced by BioPartners, was rejected by the EMA due to concerns that the applicant had not adequately demonstrated comparability to the innovator product.<sup>129</sup>

### *C. Comparability versus Interchangeability*

The structure of the EU's regulatory regime for biosimilars raises an important distinction about treating follow-ons as true generics. Fortunately, it also suggests a realistic solution. Sections 505(j) and 505(b)(2) of the Hatch-Waxman Act establish a “two path” approval

process for follow-on drugs. Under 505(j), follow-on drugs that can be shown to be identical to their reference products need undergo no clinical testing and are treated as fully interchangeable with the reference drugs. On the other hand, under section 505(b)(2), follow-on drugs that have potentially relevant differences from the reference drugs are subject to some *de novo* pre-clinical or clinical testing requirements—whereby the applicant must demonstrate that the differences pose no safety or efficacy problems—and usually are not treated as interchangeable. Manufacturers who feel confident that they can meet the true generic standard submit under 505(j), but they run the risk that their applications will be rejected if they cannot supply sufficient proof of sameness and bioequivalence.

The EU approach, on the other hand, provides just one pathway for all biosimilar applications. Manufacturers who clear the hurdle for non-generic follow-on approval may go farther and try to meet the standard for true generic approval. But a product that is not deemed sufficiently identical for a full generic approval may still be approved as a biosimilar. In the United States, on the other hand, most follow-on biotech “drugs” are likely to be submitted through the 505(b)(2) comparable-drug approval pathway. FDA has left open the possibility that it would consider a 505(j) application for a follow-on biotech drug that theoretically could be approved as a true, fully interchangeable, generic—provided that the manufacturer can demonstrate that it is identical and bioequivalent to the reference drug. But a manufacturer must choose one pathway or the other.

Critics argue that follow-on biologics should never be considered fully interchangeable with their reference product counterparts.<sup>130</sup> However, whether any given follow-on product manufacturer can or cannot demonstrate that its product is identical to the corresponding reference product is an empirical question that cannot be answered in the abstract. Although many scientists believe that the current state of the art in protein characterization is not yet sufficient to prove that two protein products generated in two different systems are identical, others disagree. However, given how rapidly the tools and methods of purification and characterization are advancing, it is not unthinkable that proving two proteins to be identical will not just be possible in coming years, but commonplace. There is no good reason to foreclose the possibility that a future follow-on biological product may be approved as a true generic, especially given the slow and deliberate nature of the legislative process. A better path would be to follow the European Union’s lead on this

issue and provide FDA with the discretion to allow interchangeability if analytical advances make true generic biologics a reality.

More importantly, experience belies the claims that no two biological products could ever be proven similar enough to establish interchangeability. There are currently several biopharmaceuticals—each produced as innovator products, not as follow-ons—that FDA already treats as functionally interchangeable. For example, there are no fewer than six approved human growth hormone products, each of which has been deemed by FDA to be identical and bioequivalent to natural growth hormone produced endogenously in human bodies.<sup>131</sup> Similarly, the protein drugs follitropin alfa and follitropin beta, which have slightly different amino acid sequences, contain FDA-approved label statements indicating that the two products are “indistinguishable.”<sup>132</sup> Neither the human growth hormones nor the follitropin products have received FDA’s highest “A” rating of interchangeability, but the examples do suggest that different products, originating from different cell lines, can be produced in such a way as to have the very high degree of structural and therapeutic similarity necessary for interchangeability.

Naturally, when determining how much original clinical data should be required to support approval of a follow-on biological product, FDA should take into consideration the complexity of a given protein’s structure, the relevance of various structural features to the protein’s therapeutic function, the amount of clinical experience with such proteins, and the extent of available scientific research and other relevant information on the proteins. And more rigorous standards should apply for the approval of true generic biologics. But, at this time, it seems clear that biopharmaceutical manufacturers have the competence to create safe and effective follow-on protein products, and that FDA has the tools necessary to distinguish between truly comparable and dissimilar products, as well as interchangeable and non-interchangeable ones.

Not surprisingly, the Schumer-Clinton and Waxman bills would create a regulatory pathway for follow-ons—called the comparable Biologic License Application (cBLA)—that preserves FDA’s discretion to determine how much scientific testing, and of what type, is necessary for the approval of a follow-on biological product. Under the cBLA pathway, a follow-on manufacturer must demonstrate to FDA’s satisfaction that there are no clinically meaningful differences between its product and the reference product, that its product and the reference product “contain

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*Creating, testing, receiving regulatory approval for, and manufacturing biopharmaceuticals are far more complex, and thus much more expensive, than producing small molecule drugs.*

highly similar principal molecular structural features,” and that its product and the reference product “utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed.”<sup>133</sup> The proposal would also create an option similar to section 505(b)(2) of the Food, Drug & Cosmetics Act, in which a cBLA applicant may rely upon “studies in the application for a reference product” so long as the follow-on product “differs from, or incorporates a change to, the reference product.”<sup>134</sup>

The bills also give FDA the discretion to consider and approve the interchangeability of a follow-on product with its reference product.<sup>135</sup> In a one-path process much like the European Union’s “biosimilar” approval track, the cBLA applicant is not required to seek an interchangeability approval, nor is FDA required to find interchangeability if the application does not include sufficient evidence to demonstrate it. But a cBLA applicant may request that FDA make an interchangeability determination while the agency considers the product for a follow-on approval.

Finally, the bills provide for a patent dispute resolution process intended to facilitate the speedy introduction of follow-on biopharmaceuticals upon the expiration of relevant patents on the innovator product.<sup>136</sup> Some observers have questioned both the need for and the appropriateness of the draft patent provisions, but they are not discussed here because those provisions are beyond the scope of this paper. It is, of course, important to protect the pharmaceutical industry’s incentives for innovation, and the Schumer-Clinton and Waxman proposals may or may not strike the most appropriate balance between access and innovation. But once the patent and data exclusivity protection for a biopharmaceutical ends, consumers would benefit from an abbreviated regulatory pathway that lets follow-on products get to market quickly. In regard to the approval pathway itself, the legislation would preserve FDA’s discretion in requesting and evaluating data submitted with a comparable biologic application. And it provides for a meaningful but flexible approval pathway for follow-on biopharmaceuticals.

## **VI. Why Approve Follow-On Biologics?**

The introduction of biopharmaceuticals in 1982 has been a huge boon to public health. Biotechnology has brought extraordinary medical advancements, helping to create medicines that treat diseases once thought to be intractable. Many forms of cancer that were invariably fatal just a

decade or two ago have now become curable. Other once-fatal diseases have become manageable, even if chronic, conditions for many sufferers thanks to biotechnology. In its brief 25-year history, the biotech industry has produced more than 187 approved medicines that have been used to treat over 300 million patients.<sup>137</sup>

But biotechnology's stunning success has come with high price. The high cost of biopharmaceutical innovation and the very strict regulatory oversight that accompanies it translate into high consumer costs. For example, an average 10-month treatment regimen of Genentech's colorectal cancer treatment Avastin can total as much as \$46,000. A full course of Celgene's multiple myeloma treatment Revlimid totals roughly \$67,000. ImClone's Erbitux costs \$10,000 per month, or about \$40,000 for a four-month course of treatment.<sup>138</sup> And Pfizer's Gentropin costs \$2,200 per month.<sup>139</sup> Americans spend roughly \$39 billion annually on biological products, and that number is expected to double in just the next few years.<sup>140</sup>

These high prices are not unwarranted, however. Creating, testing, receiving regulatory approval for, and manufacturing biopharmaceuticals are far more complex, and thus much more expensive, than producing small molecule drugs. Economists Joseph DeMasi of Tufts University and Henry Grabowski of Duke University found that the average out-of-pocket cost of developing a new biological product totals well over half a billion dollars.<sup>141</sup> But, just like conventional drugs, most biopharmaceuticals fail before ever making it to market. When expenditures on failed products and other capital costs of research and development are included, the average price of bringing a new biological product to market rises to roughly \$1.24 billion.<sup>142</sup> The high retail prices of biopharmaceuticals reflect the vast expense of developing those products. And, without such high prices, few investors would be willing to take the risks inherent in supplying capital to the biotechnology industry. The result would be fewer and fewer lifesaving medicines.

Similarly, a finite term of patent protection is an essential tool for ensuring that biopharmaceutical firms have the financial wherewithal to invent, test, and manufacture increasingly innovative new products. Nevertheless, competition remains the lifeblood of America's economy, which is why intellectual property rights are granted for a limited period. Patent protection provides an important incentive to innovators. But eventual patent expiration, and the competition it spawns, ensures that

manufacturers must always seek to innovate and economize, and it tends to generate consumer benefits in the form of higher quality and lower prices.

Some observers, such as Duke University's Grabowski, have argued that, because the biotechnology industry is much less mature and less financially stable today than the small molecule pharmaceutical industry was when the Hatch-Waxman Act was passed in 1984, and because developing biopharmaceuticals is genuinely more complex, time-consuming, and expensive than developing small molecule drugs, an extended period of data exclusivity for innovator firms is needed to protect incentives for innovation.<sup>143</sup> Under the original Hatch-Waxman Act, FDA must wait five years after approval, unless the innovator consents, before referring to the innovator's data when considering an application from a generic competitor. Several other countries also ensure limited data exclusivity, and the European Union extended this period to 10 years for biological products. According to Grabowski, extending the data exclusivity period for biopharmaceuticals in United States to 10 years "would help balance innovation incentives and price competition when instituting a new regulatory pathway for biologicals."<sup>144</sup> Such a proposal has genuine merit. But the question addressed here is whether any abbreviated approval pathway for follow-on biopharmaceuticals is warranted once the patent term or data exclusivity period expires.

Establishing a regulatory pathway for the approval of follow-on biological products could save Americans hundreds of millions, or even billions of dollars each year. Experience with generic small molecule drugs provides a crude reference point for estimating how big those cost savings may be. A 1998 Congressional Budget Office study found that generic drugs save consumers between \$8 billion and \$10 billion each year.<sup>145</sup> CBO calculated that, upon the introduction of the first generic version of a typical innovator drug, the price of that innovator drug falls by an average of 44 percent and the generic version sells for roughly 25 percent less than that. And when additional generic manufacturers enter the market with their own products, the retail price of all the generics falls to about 40 percent lower than the innovator drug.<sup>146</sup> Other researchers concluded that generic drug prices fall even further.<sup>147</sup>

Of course, there are important differences between small molecule drugs and biopharmaceuticals that will prevent the total cost savings from follow-on biologics from being as large—at least in the short term. For example, while more than a billion prescriptions, or roughly half of

all the medicines used in the United States, are filled with generic small molecule drugs every year,<sup>148</sup> biopharmaceuticals still comprise only a small portion of the total market for medicines. And, though many follow-on biopharmaceuticals could be approved in the next decade, few, if any, true generic follow-ons are likely to be approved during that period. Thus, the dollar amount of total savings is likely to be much smaller for the foreseeable future. In addition, much of the technical complexity inherent in creating and manufacturing the innovator biopharmaceuticals will carry over to the follow-on producers. Consequently, Duke University's Grabowski estimates that savings from follow-on biopharmaceuticals would be just 10 to 25 percent—significantly less than savings from traditional generic drugs—because the costs of entry will be much higher for follow-on biologics than for generic drugs and because fewer companies will be financially and technologically capable of taking on the longer and more expensive development and testing process.<sup>149</sup> Indeed, some biopharmaceuticals may see no follow-on competitor at all.

Follow-on manufacturers will save large sums, however, because they would not need to duplicate many of the costly clinical trials, and, compared with innovator firms, many fewer of their products are likely to fail before commercial approval by FDA. However, given the status of today's technology, follow-on producers are unlikely to be freed entirely from the burden of conducting some human clinical testing. So, whereas re-creating a conventional small molecule generic drug can cost as little as a few million dollars up to as much as \$30 million, some analysts have estimated that the cost of developing a follow-on biologic could be as much as or more than \$200 million.<sup>150</sup> And, unless a large number of follow-on biopharmaceuticals can be approved as interchangeable, competition between most innovators and their comparable follow-ons may be more like the competition now posed between two similar brand-name drugs than between a brand name and true generic. Such competition does put downward pressure on both competitors' prices, but the expected savings are not as great as for true generics.

Nevertheless, because many biopharmaceuticals are so expensive, even competition from a comparable follow-on biologic should be expected to cause overall prices to fall. The pharmacy benefits manager Express Scripts has estimated that follow-on biologics could save consumers of just four classes of biological products (interferons used to treat multiple sclerosis, erythropoietin used to treat anemia, growth

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hormones used to treat growth failure, and insulin for diabetes) more than \$70 billion over 10 years.<sup>151</sup> The estimate assumes that more than 80 percent of patients would be willing to move to a fully-interchangeable, or true generic biologic, and that roughly half would move to a non-interchangeable, but comparable, follow-on biologic. It also assumes that the follow-ons would be priced at just 25 percent below the innovator products, which is based on the price discount Sandoz offered for Omnitrope when it was placed on the market in Europe last year to compete with Pfizer's Gentropin.<sup>152</sup>

Another study, prepared by the law firm Engel & Novitt for the Pharmaceutical Care Management Association, estimated that the Medicare Part B program alone could save over \$14 billion over the same 10-year period.<sup>153</sup> While fewer than 20 percent of Americans receive benefits from Medicare, the top five best-selling biological products in the U.S. (Amgen's Enbrel and Aranesp, Johnson & Johnson's Remicade and Procrit, and Genentech's Rituxan) account for roughly 30 percent of Medicare Part B spending,<sup>154</sup> in large part because these products treat diseases most common among the aged. And the estimate explicitly excludes certain classes of biologics now covered by Medicare—such as follow-on products that might be approved as drugs under section 505(b)(2) of the Food, Drug and Cosmetics Act—in order to prevent over-inflating the potential cost-savings. Thus, while consumers generally could see substantial benefits from the approval of follow-on biologics, the Engel & Novitt study estimates that taxpayer-financed programs such as Medicare are likely to be among the biggest beneficiaries.

While both Express Scripts and Engel & Novitt claim to have used conservative assumptions about such variables as price discounts, utilization rates, and patent expirations, the Biotechnology Industry Organization has challenged both estimates as flawed.<sup>155</sup> For example, BIO notes that, while both studies assume a certain level of interchangeability for follow-on biologics, current technical limitations will likely preclude any follow-ons from being approved as true generics—at least in the coming decade. BIO also indicates that patent expirations for many of the most widely used biopharmaceuticals are likely to be much farther in the future than is assumed by the Express Scripts and Engel & Novitt reports, and BIO notes that it seems implausible to believe that “for every biologic that comes off patent there will be an associated follow-on [product].”<sup>156</sup>

Many of BIO's criticisms of the Express Scripts and Engel & Novitt cost savings estimates are valid, and the authors of each recognize inherent limitations in the available data. Nevertheless, while a fully accurate estimate of the potential cost savings from follow-on biopharmaceutical approvals may be impossible to derive, it is not at all implausible to assume that those savings are likely to be substantial. Even if no follow-on products were approved as interchangeable generics, if market penetration were as low as 20 percent, and if the offered discounts were as little as 10 or 15 percent, annual savings could well total hundreds of millions of dollars each year for the small handful of biopharmaceuticals expected to come off patent in the coming decade. And, according to some analysts, as many as 75 currently approved biopharmaceuticals are likely to be eventual targets for follow-on production.<sup>157</sup> This may represent just a small portion of the \$39 billion-a-year biologics market in the United States, but the possibility of a few hundred million dollars of cost savings to consumers, insurers, and taxpayers, should not be dismissed so lightly.

## **VII. Conclusion**

With such substantial cost savings at stake, it is no wonder that advocates of follow-on biologics are so eager for FDA to implement an abbreviated regulatory pathway. Similarly, having invested billions of dollars and decades of effort in the creation of such important life-saving technologies, it is no wonder that the innovator biotechnology firms have become so concerned about the possibility of competition from inexpensive knock-offs. The biotech industry can be forgiven for its zeal in protecting its intellectual property. Millions of lives have been saved or enhanced by innovator products, and it is appropriate that limited periods of patent protection and data exclusivity be available to ensure that biopharmaceutical firms have the financial wherewithal to invent, test, and manufacture increasingly innovative new products. Nevertheless, competition also benefits consumers, and competition in the biopharmaceutical market could eventually be worth billions of dollars each year.

Most importantly, generic manufacturers have the competence to create safe and effective follow-on protein products, and FDA has the tools necessary to distinguish between truly comparable and dissimilar products, as well as interchangeable and non-interchangeable ones. At this time, it is not technically feasible for all biopharmaceuticals to be reproduced

faithfully, but FDA and regulators around the world have already acknowledged that advances in protein characterization and purification make it technically feasible to compare the safety and purity of many proteins arising from two different manufacturing processes. And FDA will continue to have a substantial amount of discretion to determine how much data, and in what form, it would require manufacturers to submit in support of new product applications. Whether it is done administratively or through new statutory authorization, creating a regulatory pathway for follow-on biopharmaceuticals would be a constructive way to advance competition in the biotechnology industry and to begin taming the rapidly increasing price of biotech medicines.

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## About the Author

Gregory Conko is a Senior Fellow at the Competitive Enterprise Institute (CEI). His research at CEI focuses on issues of food and pharmaceutical drug safety regulation, with an emphasis on biotechnology and genetics. Mr. Conko's book, *The Frankenfood Myth: How Protest and Politics Threaten the Biotech Revolution* (Praeger, 2004), co-authored with Henry I. Miller, was named by *Barron's* as one of the 25 best books of 2004. His other writings have appeared in such journals as *Nature Biotechnology*, *Transgenic Research*, *Politics and the Life Sciences*, and the *Richmond Journal of Law & Technology*, and in such newspapers as the *Financial Times*, *Wall Street Journal Europe*, *Asian Wall Street Journal*, *Los Angeles Times*, and *San Francisco Chronicle*. Mr. Conko is also a co-founder and Vice President of the Auburn, Alabama-based AgBioWorld Foundation. He is a member of the Board of Scientific and Policy Advisors for the New York-based American Council on Science and Health. And, in 2006, he was named by the journal *Nature Biotechnology* to its short list of "Who's Who in Biotechnology." He holds a B.A. in Political Science and History from the American University, and he is currently pursuing a J.D. at the George Mason University School of Law, where he was recently Articles Editor of the *Journal of Law, Economics & Policy*.

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