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MEMBER BRIEFING

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Where Are All the Generic Biopharmaceuticals (Follow-On Biologics)? (And How Much Money Will They Save?)

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Introduction

A toy plane has a handful of parts. A Boeing 747 has several millions. This makes sense: toy planes are small, simple models, while 747s are large, high-performance aircraft that travel more than 500 mph with thousands of component systems acting together. The toy costs a few dollars because it is easy to manufacture.[1] The 747 costs about $225 million because of its highly complex nature, testing, and the need to ensure safety. This comparison is worth keeping in mind as the debate heats up on generic biopharmaceuticals.[2]

Biopharmaceuticals are one of the fastest growing—and most expensive—categories of drugs. The Food and Drug Administration (FDA) issued marketing approval on 36 biopharmaceuticals in 2002; it also approved 37 in the following year, 40 in 2004,[3] and 38 in 2005.[4] Biopharmaceutical approvals are predicted to grow at a rate of 16–30%, compared with an approximate 4% growth of traditional small-molecule drugs.[5] As of May 2006, 111 biopharmaceuticals were in late-stage development in 190 indications—including 87 new molecular entities, 25 that had completed Phase III trials,

and 24 that already had FDA approval in other indications.[6] Many more new biopharmaceuticals reportedly are in the approval process.[7]

Most biopharmaceuticals are dispensed through a specialty pharmacy system. The four biopharmaceuticals accounting for the majority of sales are erythropoietin (e.g., Epogen®, Procrit®, and Aranesp®), recombinant DNA insulin (e.g., Humulin® and Novolin®), human growth hormone (e.g., Saizen® and Somatropin®) and granulocyte colony stimulating factors (e.g., Neupogen®, Neulasta®, and Leukine®). Costs of these biopharmaceuticals exceed that of traditional small-molecule drugs, whose cost rose by 6% in 2006 while spending on specialty biopharmaceuticals increased by 21%.[8]

Single-source biopharmaceuticals have the potential to present important new pressures on the federal budget.[9] Congress has voiced concern over drug cost increases and is concerned with the possibility that competing low-cost substitutes to the brand-name biopharmaceuticals might not be available when the patents expire.[10] As a result, several bills introduced over the past two years would create an expedited marketing approval pathway for follow-on biologics (FOBs),[11] paving the road for a policy change that will someday allow for an easier process to approve these FOBs.

This Member Briefing will explore the viability of approving FOBs and discuss how allowing an expedited process might reduce costs of these expensive biopharmaceuticals. First, it will define biopharmaceuticals. Next, it will review the science of biopharmaceuticals. Then it will explore the regulatory framework. It will also review the issues surrounding FOBs. Additionally, it will summarize the bills pending in Congress. Finally, it will explore the potential economic impact of creating a new framework for expedited approval of FOBs.

I. What are Biopharmaceuticals?

A. Biological Products

Biological products are proteins that are made by recombinant DNA technology. They function as a drug and carry many names, including biopharmaceuticals, biotech drugs, biological products, or therapeutic biological products.[12] For the purpose of this paper, we will refer to them as biopharmaceuticals.

The term *biological product* is defined in the Public Health Services Act (PHSA)[13] as a product comprised of a biological product that is derived from and produced in living materials (e.g., microbial cells, mammalian cell lines, plant cell cultures, transgenic animals, or plants) and "are intended for use in the prevention, treatment or cure of a disease or condition in human beings." [14]

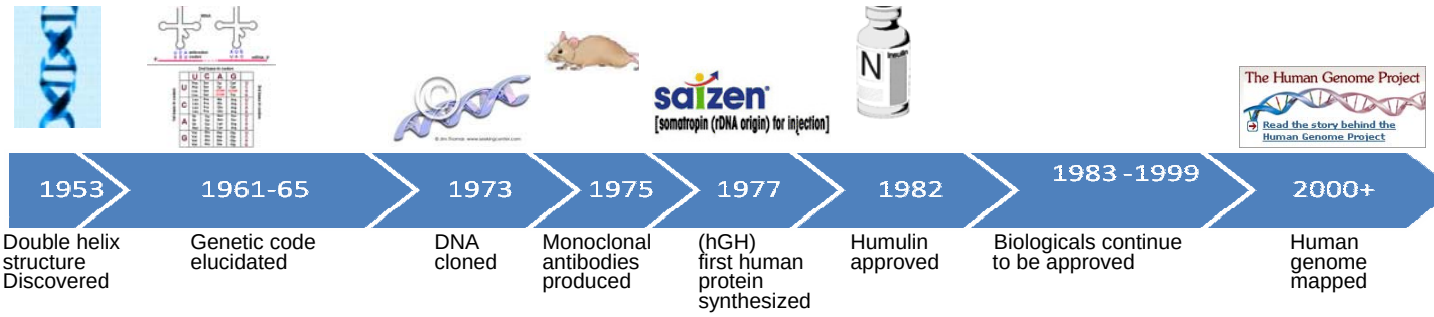
This definition overlaps with that for drugs. The term *drug* includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals."[15] As a result, biopharmaceuticals are considered both "biological products," which are regulated under the PHSA, and "drugs," which are regulated under the Food Drug & Cosmetic Act (FDCA). We will discuss the regulatory scheme for biopharmaceuticals in Section III of this paper, but first look back at the evolution of the biopharmaceutical industry.

B. History of Biopharmaceuticals

Although the first biopharmaceutical was approved in 1982, modern biotechnology began in 1953 when Watson and Crick revealed the three-dimensional structure of DNA.[16] Over the next thirty years, new breakthroughs and techniques such as cell-culturing, synthesis of nucleic acids, understanding of how DNA is replicated, how DNA and RNA work, and gene cloning were discovered. In 1961, the genetic code

was understood for the first time and, in 1967, the first automatic protein sequencer was perfected.

Figure 1



In 1973, Cohen and Boyer perform the first successful recombinant DNA experiment, using bacterial genes, and in 1975 the first monoclonal antibodies are produced. Two years later, genetically engineered bacteria were first used to synthesize human growth (hGH) protein.[17] In 1982 Humulin®, Genentech's human insulin, was produced by genetically engineering bacteria.[18] Since that time, more than one hundred biopharmaceuticals have been approved by the FDA and are being marketed in the United States. In 2006, worldwide biopharmaceutical sales were more than $64 billion.[19] The biopharmaceuticals listed in Table 1 were the 20 largest selling biologic drugs in 2006, accounting for $49.4 billion in sales worldwide.[20]

Table 1

2006	Name of Biologic	2005
1	Enbrel	1
2	Aranesp	3
3	Rituxan	4
4	Remicade	5
5	Procrit	2
6	Herceptin	9
7	Epogen	6
8	Neulasta	7
9	Novolin	
10	Avastin	13
11	Lantus	11
12	Humira	12
13	Levemir	
14	NeoRecormon	8
15	Avonex	10
16	Rebif	14
17	Neupogen	15
18	Humalog	16
19	Betaseron	20
20	Pegasys	18

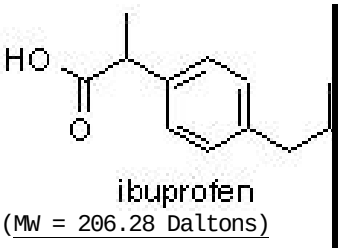
II. The Science of Biopharmaceuticals

A. Not Just Your Old Biochem Class

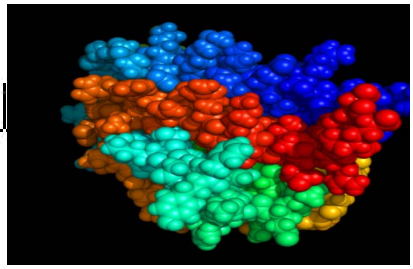
Many scientific disciplines contribute to biotechnology: molecular biology, microbiology, biochemistry, genetics, chemical engineering, and cell biology.[21] The traditional medicines (often called small-molecule drugs)—historically the mainstay of medical, nursing, and pharmacy school education about drugs—are synthetic small molecules produced through chemical processes. They are discovered through high-throughput screens of tens of thousands of randomly generated compounds. On the other hand, biopharmaceuticals are macromolecules that are produce by living systems and created from amino acids and nucleic acids.

B. Synthetic Versus Biotechnology-derived Medicinal Products

Biopharmaceuticals are generally much more complex than small-molecule drugs, and their manufacture often entails the use of live cells and complicated biologic processes.[22] The proteins are usually substantially large, complex molecules that may be mixtures of distinct entities.[23] For example, in Figure 2, we compare ibuprofen to erythropoietin. Ibuprofen's structure ($C_{13}H_{18}O_2$) is relatively simple and may be depicted with a simple diagram. It has a molecular weight of 206.28 Daltons and is synthesized chemically from isobutyl benzene.[24]



ibuprofen
(MW = 206.28 Daltons)



Erythropoietin (34,000 Daltons)
Polymer: 1 ERYTHROPOIETIN ; Mutation: N24K, N38K, N83K, P121N, P122S;
Chain: A
Polymer: 2 EPO RECEPTOR
Fragment: EXTRACELLULAR DOMAIN
Mutation: N52Q, N164Q, A211E ;
Chains: B,C

Figure 2

On the other hand, erythropoietin (EPO), a glycoprotein hormone (a cytokine), is produced by recombinant DNA technology in mammalian cell culture. Its molecular description is much more complex.[25]

The process under which biopharmaceuticals are made is almost equally important to the structure of the drug. Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variations in the manufacturing process. The quality and nature of natural source products can vary depending on condition of the source material, processes used to extract and purify the product, and other factors.[26]

III. Regulatory Framework for Biologics

A. Timeline

Biologics were regulated in the United States four years before the federal government began to regulate drugs.[27] In 1902, the Biologics Controls Act was passed in response to contaminated smallpox vaccines. The Act allowed the federal government to license and inspect facilities that were manufacturing biologics.[28] The statute was later re-codified into the PHSA[29] in 1944, and licensing of the biological products themselves was also required. Generally, from 1944 to 1972 both biologics and the manufacturing facilities were regulated by the National Institutes of Health (NIH). However, in 1972, the responsibility for regulating biologics was turned over to the FDA's Center for Biologics Evaluation and Research (CBER).

In 1997, the Food and Drug Administration Modernization Act (FDAMA) replaced the dual licensing (facility and product) with a new single licensing system: the Biologics License Application (BLA). Since June 2003, the responsibilities for regulating biologics have been divided between CBER and the FDA's Center for Drug Evaluation and Research (CDER). However, all licensing is through the NIH under the PHSA.[30] See

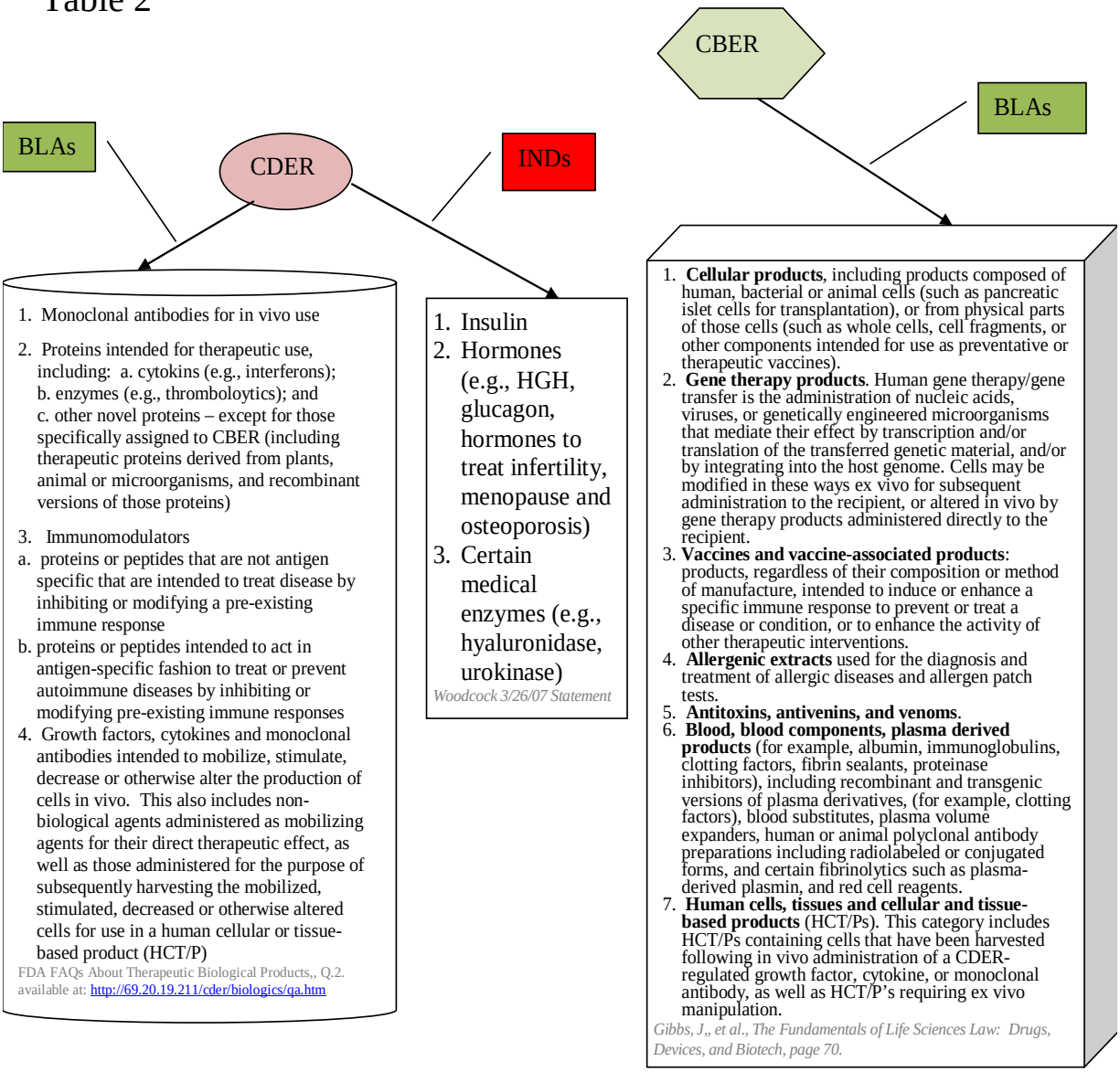
Table 2 for a flow chart describing how different biopharmaceuticals are licensed and regulated.

B. Current Biopharmaceutical Approval Process

Regardless of whether a biopharmaceutical will be regulated by CBER or CDER, the regulatory review and approval standards are identical. Further, the development processes are similar, going through basic research, preclinical studies (using laboratory animals) to evaluate toxicity, pharmacokinetics, and pharmacodynamics.[31] After preclinical (animal) studies, the development of the biopharmaceutical continues with clinical studies. As with other drugs, the manufacturer must submit an Investigational New Drug Application (IND) to the FDA before instituting human subject clinical trials. If the FDA concludes that the proposed clinical study can be conducted without imposing unreasonable risk to the human subjects, and that the study is properly designed to establish efficacy of the biopharmaceutical, the FDA will grant an IND.

Biological Proteins

Table 2



Clinical trials must follow specific quality assurance requirements[32] and will go through three phases to demonstrate the safety, purity, and potency of the biologic for the proposed indication. Once clinical trials are completed, the manufacturer will submit a Biologics License Application (BLA) to the FDA[33] to establish the efficacy, safety, purity, and potency of the biologic for the proposed indications and to show that its

manufacturing facilities comply with the current good manufacturing practice requirements.[34]

IV. FOBs

FOBs—also called biosimilars, biogenerics, biopharmaceuticals, follow-on proteins, or biocomparable proteins[35]—may be a way to greatly reduce rising drug prices. The term FOBs generally refers to protein and peptide products that are intended to be similar enough to an already approved biopharmaceutical so that the follow-on manufacturer can rely on certain existing scientific knowledge about the safety and effectiveness of the biopharmaceutical.[36]

Given the large costs associated with the development and clinical testing of a biopharmaceutical, the manufacturer of such a product almost always will obtain patent protection for the product before investing in testing and the FDA approval process. Because of the long approval process, most manufacturers will have only 7–12 years of market exclusivity provided by the patent. Once the patent expires, other manufacturers would conceivably be free to seek approval to manufacture the product. Some biopharmaceutical patents have already expired. A number of others are due to expire in the next few years.[37]

However, the potential opportunity for price reductions versus the originator biopharmaceuticals remains to be determined, as the advantage of a slightly cheaper price may be outweighed by the hypothetical increased risk of side-effects from FOBs that are not exact copies of the originator protein.[38]

A. The Drug Price Competition and Patent Term Restoration Act of 1984

All drugs and biopharmaceuticals must have either a new drug application (NDA) or a BLA approved before they may be marketed in the United States.[39] Historically, generic drug manufacturers would need to file a complete NDA before marketing their products—making it a difficult, cumbersome, and expensive process to bring a generic to market. [40]

In an effort to make it simpler for generic products to be introduced into the market, two alternative shorter processes were created by the Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act) in 1984.[41] Section 505(j)[42] created the abbreviated new drug application (aNDA) process. Using the aNDA process, a generic manufacturer seeking to market a product having the same active ingredient, route of administration, dosage form, and strength as the brand-name drug may rely on the safety information from the original manufacturer. This allows for generic companies to seek approval by showing bioequivalence prior to the innovator's patent expiring, so that the generic drug can be available on the day the patent expires.[43]

A second abbreviated process exists for products that do not have the same active ingredient, route of administration, dosage form, or strength. Under Section 502(b) (2),[44] drugs that either differ from an approved innovator product or require additional human studies for approval may rely upon safety and efficacy studies performed by others such as the original manufacturer.

As discussed above, biopharmaceuticals are considered to be "drugs."[45] Therefore, theoretically this second pathway could apply to biopharmaceuticals allowing

a shortened approval process for FOBs. However, the FDA has only applied 505(b)(2) pathway to those biopharmaceuticals that have been regulated as drugs under the FDCA, such as human growth hormone, [46] taking the position that additional legislation is required to provide such a pathway for those biopharmaceuticals that are licensed as "biologics" under the PHSA.[47]

B. Generic Substitution

After the FDA approves a generic, the question of whether it is generically substitutable is a matter of state law. Generally, a drug may be generically substituted when it: (1) has the identical amount of the same active chemical ingredients; (2) is in the same dosage form; (3) meets applicable standards of strength, quality, and purity according to a nationally recognized compendium; and (4) if administered in the same amounts will provide comparable therapeutic effects.[48] The states differ on how they determine which products are generically equivalent. Some states have a "positive formulary" that lists all of the products that may be generically substituted in that state.[49] Others have a "negative formulary,"[50] which lists those drugs—generally narrow therapeutic index (NIT) drugs[51]—that may not be substituted. Others default to the FDA's determination of whether the product is bioequivalent.[52]

For those states that allow generic substitution according to the FDA's determination of bioequivalency, pharmacists must consult the FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book).[53] The Orange Book identifies approved drug products except for those drugs covered by the ongoing Drug Efficacy Study Implementation (DESI) review

(e.g., Donnatal® tablets and Librax® capsules) or pre-1938 drugs (e.g., Phenobarbital tablets).

In addition, the list contains therapeutic equivalence evaluations for approved multisource prescription drug products. In general, drugs that are A or AB rated are generically substitutable.[54]

C. Difficulty with Generic Biopharmaceuticals

Because it will be difficult to show bioequivalency, biopharmaceuticals will most likely not be A or AB rated. Pharmacists therefore will not automatically be able to generically substitute similar products. With small molecular products, there is a long history to support the use of various scientific approaches to establishing bioequivalence between products with the same active ingredient(s) produced by different manufacturers. [55] We know now that these bioequivalent[56] products can generally be expected to behave in a pharmacologically interchangeable manner when used in patient care. [57] With biopharmaceuticals, the FDA has not determined how interchangeability can be established for complex proteins.[58]

Because of the variability and complexity of protein molecules, the FDA believes that current limitations of analytical methods—and the difficulties in manufacturing a consistent product—make it unlikely that, for most biopharmaceuticals, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.[59] This is because while the patent lists the ingredients, the manufacturing process for the product is likely protected as a trade secret.[60]

One alternative is to use the safety and effectiveness data of an already-approved biopharmaceutical. This could be done by extending the 505(b)(2) process to

all biopharmaceuticals, including those that have been issued a BLA. However, demonstrating the similarity of a FOB is more complex and requires more new data than is needed to determine whether a manufacturing change will affect the product.[61]

In general, the required new data will be influenced by the extent to which the FOB can be demonstrated to be sufficiently similar (structurally, functionally, and clinically) to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product.[62] In addition, the amount and type of new data needed will be influenced by the clinical use of the product and the amount and type of clinical experience that has been accumulated about the approved product as well as related products.[63]

Current technologies such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein, making the current method of evaluating equivalence fraught with uncertainties.[64] Thus, predicting the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product.[65]

The most critical safety concern relating to biopharmaceuticals is immunogenicity.[66] All biopharmaceuticals are biologically active molecules derived from living cells and have the potential to evoke an immune response. Although the immunogenic potential cannot be predicted through chemical or structural analyses of the biopharmaceutical, several factors are known to affect a product's immunogenic

potential. The presence of impurities in the final product, structural modifications as a result of the manufacturing process, or storage conditions can increase immunogenicity.[67]

V. Current Legislative Initiatives

There are four bills proposed in the 110th Congress to create an expedited marketing approval pathway for "comparable" biologics.[68] The Access to Life-Saving Medicine Act, introduced as H.R. 1038 and S. 623,[69] would amend the PHSA[70] to allow the FDA to determine, on a case-by-case basis, what studies were necessary to establish comparability. Under this bill, the FOB manufacturer would have to prove that the FOB had a comparable principal structure to the innovator drug. Similar to the aNDA process, the FOB would be required to have the same mechanism of action (if the mechanism of action for the innovator product is known, the same administration route, dosage form, and strength).[71]

The Patient Protection and Innovative Biologic Medicines Act of 2007 would require the FDA to publish guidance documents for various classes of biological products setting forth what data and information would be required to be filed before approving the FOB.[72] Similarly, the Affordable Biologics for Consumers Act would require the FDA to develop guidance.[73]

An additional bill, S. 1695, is titled the Biologics Price Competition and Innovation Act of 2007. Under S. 1695, a FOB may be designated as either a "biosimilar" or an "interchangeable" product. In general, under S. 1695 a follow-on product is biosimilar if (1) analytical, animal, and clinical studies show that it is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, (2) the two

products have the same mechanism of action, (3) the condition of use in the proposed product has been previously approved for the reference product, and (4) the route of administration, dosage form, and strength of the two products are the same.[74] A follow-on product is interchangeable if (1) it can be expected to produce the same clinical result as the reference product in any given patient and (2) the risk, in terms of safety or diminished efficacy or switching between the two products, is not greater than the use of the reference product without such alternation.[75] It is unlikely that the 110th Congress will pass any of these bills, but this is likely to be a hot topic beginning in 2009.

VI. How Much Money Will FOBs Save?

Will the follow-ons be cheaper than the originals? To some degree, that depends on Congress and whether a resulting law requires limited or extensive clinical trials. What cannot be legislated away is the high cost of producing biopharmaceuticals.[76] Even if Congress passes a bill creating a method to approve FOBs, the follow-ons most likely will not be generically substitutable. A finding of safety and efficacy is distinct from determining that the FOB would be substitutable (e.g., A or AB-rated) for the innovator biopharmaceutical.

In addition to not being generically substitutable, a follow-on manufacturer would need to engage in additional tests to demonstrate that the two products would be therapeutically substitutable. This would requiring showing that switches between the products would not negatively affect the safety or effectiveness of the products as a result of immunogenicity. For many follow-on protein products—and in particular, the more complex proteins—repeated switches between products may negatively impact

safety or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.[77]

Protein drugs require living cells and a delicate, very expensive manufacturing process that pushes the cost of developing a new drug (even a look-alike) to $200–300 million—less than the average $900 million you need to launch an original drug.[78] But it is much more than what it costs to copy a simple molecule like the one in Zocor or Zantac.

It is unclear how much savings developing a FOB abbreviated pathway will yield. One recent study estimated a savings over a ten-year period of approximately $71 billion.[79] Another study estimated that Medicare Part B (which pays for drugs such as chemotherapy which are administered at a physician's office) could save approximately $14 billion from 2007 to 2017.[80] Another study estimated savings would be only $3.6 billion over the next 10 years.[81]

Critics have said that these estimates may be overstated,[82] because of the more expensive manufacturing process than small molecule drugs[83] and the need for the follow-on manufacturer to engage in costly marketing including hiring salespeople to educate the prescribers about the interchangeability.[84] Because FOBs will most likely not be A- or AB-rated generics, making them similar to narrow therapeutic index drugs, pharmacists will need to contact physicians for a new prescription if a patient requests—or their health plan encourages—that the FOB be dispensed. Although a FOB may prove to be as safe as the originator product, switching the patient between products will need to be handled with caution.[85] Manufacturers, physicians, and pharmacists will

need to provide information to patients and their caregivers so that they can assess the risks involved in switching from an established product to a FOB.[86]

Further, biopharmaceuticals tend to have smaller target markets for which incentives to entry may not be as high, and they tend to be used to treat life-threatening diseases, for which managed care organizations are often less likely to utilize price control measures.[87] As a result, some economists argue that very few FOB companies are likely to emerge, making price drops for consumers unlikely to utilize price control measures.[88] Historically, when there are only a small number of generic drugs available, prices generally do not go down very much. For example, the average price reduction for a generic that has been granted 180-day exclusivity[89] is only 30%, as compared to a 70% amount for multisource generics[90].

On example of disappointing discounts is Omnitrope,™ a biosimilar version of Pfizer's human growth hormone (HGH) Genotropin.® Omnitrope was launched under special rules in Europe and the U.S. several years ago by Novartis' Sandoz subsidiary. The first biosimilar to reach patients in the developed world, it has captured less than 1% of the $831 million European HGH market. Aitken attributes this performance to the conservatism of doctors, as well as issues around its delivery mechanism. Also, the price is only 20–25% below that of the patented version as opposed to 50–70% below for traditional generic medications.[91]

However—even if savings from FOBs turn out to be far less than some predict—there are many for whom the savings are important, such as legislators who are struggling with the deficit and the increase in federal healthcare program costs, as well

as patients.[92] It will be interesting to watch the evolution of FOBs, how they will improve patient care, decrease overall drug spending, and help the world.

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[1] Bryan Liang, *Don't Compromise the Safety of Biotech Drugs*, LA Times (4/28/08).

[2] *Id.*

[3] Schacht, W., *Follow-On Biologics: Intellectual Property and Innovation Issues (CRS Report for Congress)*, Jan. 17, 2008. Page CRS-1 (hereinafter, Schacht, FOBs).

[4] Biotechnology Industry Organization Press Release *Biotechnology Industry Ends 2005 with Breakthrough Product Approvals and Steady Financing*, (1/18/2006), *available at* www.bio.org/news/newsitem.asp?id=2006_0118_02.

[5] Paul C. Nagle, Christopher A. Nictia, Leslie A. Gerdes, Cynthia Schmeichel, *Characteristics of and Trends in the Late-stage Biopharmaceutical Pipeline*," Am.J. of Managed Care, Vol 14, No. 4, P. 226 (April 2008) (hereinafter, "Nagle et. al, Characteristics of and Trends"), *citing*, Cowen and Company LLC*., Therapeutic Categories Outlook*. New York, NY: Cowen & Co LLC; October 2007; Simon F. *Market access for* biopharmaceuticals: new challenges. Health Aff (Millwood) 2006; 25(5):1363-1370; Mullins CD, DeVries AR, Hsu VD, Meng F, Palumbo FB. *Variability in growth in spending for outpatient specialty pharmaceuticals*. Health Aff (Millwood). 2005;24(4):1117-1127 *available at* http://ajmc.com/Article.cfm?Menu=1&ID=10172.

[6] *Id*.

[7] Kerry A. Dolan, *Biology Rising*, Forbes.com, May 12, 2006, *available at*: www.forbes.com/2006/05/12/merck-pfizer-amgen-cz_kd_0512biologics_print.html.

[8] Miller, S. & Houts, J, *Potential Savings of Biogenerics in the United States,* (Feb. 2007), *available at* www.express-scripts.com/industryresearch/outcomes/onlinepublications/study/potentialSavingsBiogenericsUS.pdf. The analysis was based on prescription drug use for two samples of three million unique Express Scripts customers in 2005 and 2006 (Hereinafter, "ESI Study").

[9] Richard G. Frank and Joseph P. Newhouse*, Should Drug Prices Be Negotiated Under Part D Of Medicare? And If So, How?*, Health Affairs 27, no. 1 (2008): 33-43 January, 2008 – February, 2008.

[10] Schacht, FOBs., page i.

[11] The Access to Life-Saving Medicine Act (H.R. 1038 and S. 623); The Affordable Biologics for Consumers Act (S. 1505 and HR. 1956); and Biologics Price Competition and Innovation Act of 2007 (S. 1695) would proscribe how products could be interchangeable.

[12] Rader, R., *What is a Generic Biopharmaceutical? Biogeneric? Follow-on Protein? Biosimilar? Follow-on Biologic?* Bioprocess International, May 2007 at p. 20.

[13] The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. 42 USC 262(i) (Sept. 27, 2007).

[14] Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

21 CFR § 600.3(h).

[15] 21 USC § 321(g)(1)(B).

[16] Robert Wright, *James Watson & Francis Crick: It took an ex-physicist and a former ornithology student — along with some unwitting help from a competitor — to crack the secret of life,* Time Magazine (March 29, 1999).

[17] *History of Biotechnology Events – Timeline*, *available at* www.biotechinstitute.org/what_is/timeline.html.

[18] *Id.*

[19] *Biological Drug Report – Top 20 Biologics in 2006*, *available at* www.biologicdrugreport.com/leading.htm.

[20] *Biological Drug Report – Top 20 Biologics in 2006, available at* www.biologicdrugreport.com/leading.htm. (Note that not all of the biologics on the list are yet approved for sale in the United States.)

[21] Grace ES. *Biotechnology Unzipped. Promises and Realities*. 2nd edition. 2006.

[22] Frank, R., *Regulation of Follow-on Biologics*, N.Engl.J.Med. 357;9 (Aug. 30, 2007) at page 842.

[23] Statement of Janet Woodcock, M.D., before the U.S. House of Representatives Committee on Oversight and Government Reform (Mar. 26, 2007) (hereinafter, "Woodcock Statement").

[24] Remington's Pharmaceutical Sciences, 17th Ed. (1985), p. 117.

[25] RCSC Protein Data Bank, *available at* www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1eer.

[26] Woodcock Statement.

[27] The first significant federal legislation of drugs was enacted on June 20, 1906, with the passing of the Wiley-Heyburn Act of the Pure Food and Drug Act, which took effect in 1907.

[28] ch. 1378, 32. Stat. 728 (1902).

[29] 42 USC 262.

[30] 68 Fed. Reg. 38067 (6/26/03).

[31] Gibbs, J. et al., *The Fundamentals of Life Sciences Law: Drugs, Devices, and Biotech*, p. 71.

[32] *See, e.g.*, 21 C.F.R. Part 58.

[33] Note that non-biotech drugs will submit a new drug application (NDA).

[34] FDA's *Frequently Asked Questions About Therapeutic Biological Products*, question #4, *available at* http://69.20.19.211/cder/biologics/qa.htm.

[35] Rader, R., *What Is a Generic Biopharmaceutical? Biogeneric? Follow-on Protein? Biosimilar? Follow-on Biologic?*, BioProcess International (May 2007), at 20.

[36] Omnitrope (somatropin [rDNA origin]) Questions and Answers, *available at* www.fda.gov/cder/drug/infopage/somatropin/qa.htm.

[37] Roger, S. and Mikhail, A., *Biosimilars: Opportunity of Cause for Concern?*, J. Pharm Pharmaceut Sci 10(3): 405-410 (5/18/07).

[38] *Id.*

[39] 505 of FDCA, 351 of PHS.

[40] Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 Food & Drug L.J. 187 (1999).

[41] PL 98-417 (S 1538) September 24, 1984.

[42] 21 USC § 355(j)(1) (2006).

[43] 1999 Guidance on 505(b)(2).

[44] 21 U.S.C. § 355(b)(2) (2004).

[45] *See supra,* note 15.

[46] In fact, this method has been used by several manufacturers to approve certain FOBs such as recombinant Hylenex® (hyaluronidase recombinant human), Hydase® and Amphadase® (hyaluronidase), and Fortical® (calcitonin salmon recombinant) Nasal Spray, GlucaGen®(recombinant human glucogon), and human growth hormone (Omnitrope® and Valtropen®). *See,* Omnitrope (somatropin [rDNA origin]) Questions and Answers, *available at* www.fda.gov/cder/drug/infopage/somatropin/qa.htm and "Stealth" Follow-on Protein Approval by FDA?, retrospective commentary on Generic BIOPHARMA website, *at* www.followonproteins.com/.

[47] Johnson, J., *CRS Report for Congress: FDA Regulation of Follow-On Biologics* (Aug. 6, 2007), page CRS-7.

[48] *See, e.g*, Ala. Code § 34-23-8(1); Az. Rev. Stat. § 32-1963.01.

[49] *See, e.g.* D.C. Code Ann. §§ 33-731, 33-733.

[50] *See, e.g,* Fla. Stat. 465.025.

[51] A list of so called narrow therapeutic index drugs was prepared by the Center for Drug Evaluation and Research in order to assist the FDA District Offices in their testing program that came about because of problems with the generic industry in the late 1980's. This working list of drugs is also currently being used as one of the factors to determine if an in vivo study or other data are needed to determine the impact of post-approval changes in the manufacture of a drug product. The list is in the "Scale-Up and Post-Approval Changes for Intermediate Release Products" (SUPAC-IR)," *available at* www.fda.gov/cder/guidance/cmc5.pdf.

[52] *See, e.g.* Haw. Rev. Stat. § 328-92.

[53] The Electronic Orange Book is accessible online *at* www.fda.gov/cder/ob/default.htm.

[54] "A" rated products are those drugs that are considered to be therapeutically equivalent to other pharmaceutically equivalent products in the Orange Book. "A" rated products are designated AA, AN, AO, AP or AT, depending on the dosage form. "AB" rated products are those drugs that the FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products when actual or potential bioequivalence problems have been resolved with adequate *in vivo* or *in vitro* evidence supporting bioequivalence.

[55] U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (September 1, 2006), *available at* www.fda.gov/cder/news/biosimilars.htm. (Hereinafter, "U.S. FDA Considerations.")

[56] The FDA defines "Bioequivalent Drug Products" as "pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. "Bioavailability" means "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." 25th Edition ORANGE BOOK, pp. vii - viii.

[57] U.S. FDA Considerations.

[58] *Id*.

[59] Woodcock Testimony.

[60] Bruce S. Manhein, Jr. Patricia Granahan, Kenneth J. Dow, "*Follow-On Biologics: Ensuring Continued Innovation in the Biotechnology Industry*," Health Affairs (March- April 2006) 25, no. 2 (2006): 394-404 *at* 397.

[61] Woodcock Testimony.

[62] *Id.*

[63] *Id.*

[64] *Id.*

[65] *Id.*

[66] H. Schellekens, *Biosimilars: Opportunity or Cause for Concern? Citing H. Schellekens. Bioequivalence and the immunogenicity of biopharmaceuticals,* Nat Rev Drug Discov, 1:457-462, 2002. M. Kessler, D. Goldsmith, and H. Schellekens*, Biosimilar therapeutic agents: issues with bioequivalence and immunogenicity*, Eur J Clin Invest, 34:797-799, 2004. H. Schellekens and N. Casadevall, *Immunogenicity of biopharmaceuticals*, Nephrol Dial Transplant, 21 Suppl 5:v9-v12, 2006.

[67] *Biosimilars: Opportunity or Cause for Concern*? Note 37.

[68] Schacht, FOBs at CRS-10.

[69] HRS 1038 and S.623.

[70] PHSA.

[71] H.R. 1038 at § 3; S. 623 at § 3.

[72] H.R. 1956.

[73] S.B. 1505.

[74] Schacht, FOBs at CRS-10.

[75] Schacht, FOBs at CRS-10.

[76] Needle Work, (Forbes) Matthew Harper 03.10.08.

[77] Woodcock Testimony.

[78] Needle Work, (Forbes) Matthew Harper 03.10.08.

[79] Miller, S. & Houts, J, *Potential Savings of Biogenerics in the United States,* (Feb. 2007), *available at* www.express-scripts.com/industryresearch/outcomes/onlinepublications/study/potentialSavingsBiogenericsUS.pdf. The analysis was based on prescription drug use for two samples of three million unique Express Scripts customers in 2005 and 2006 (the ESI Study).

[80] Engel & Novitt, *Potential Savings That Might Be Realized By the Medicare Program from Enactment of Legislation Such As the Access to Life-Saving Medicine Act (H.R. 6257/S. 4016) that Establishes a New cBLA Pathway for Follow-On Biologics*, (the "PCMA Study")

[81] Avalere Health, LLC study (cited in PhRMA statement on FOBs).

[82] A February 2007 article authored by the Director of Economic Policy for the Biotechnology Industry Organization, the trade group for innovator biopharmaceutical manufacturers, identified nine analytical flaws in the ESI Study and the PCMA Study, chief among them being a presumption that a FOB pathway would generate the same savings as generic drugs, market penetration rates for FOBs, assumptions about patent expiration, calculation errors in the PCMA study, internally inconsistent allegations of interchangeability in the ESI study, and calculations based on unsupported determinations of interchangeability. Ted Buckley, "Recent Studies on Follow-On Biologics are Based on Seriously Flawed Assumptions," (Feb. 22, 2007: *available at* www.bio.org/news/newsitem.asp?id=2007_0222_04).

[83] Schacht, FOBs, at CRS-21.

[84] Schacht, FOBs, at CRS-23.

[85] Biosimilars: Opportunity or Cause for Concern? Note 37.

[86] Biosimilars: Opportunity or Cause for Concern? Note 37.

[87] Kathleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 Mich. Telecomm. & Tech.L Rev 245 (2007), *available at* www.mttlr.org/volfourteen/kelleher.pdf, *citing*, Stephan Herrerra, *Biogenerics Standoff*, 22 Nature Biotechnology, 1343, 1345 (Nov. 2004).

[88] *Id.*

[89] Generics manufacturers are rewarded for successfully challenging a patent: the first firm that files an Abbreviated New Drug Application is granted 180-day products. Richard G. Frank, Ph.D., *The Ongoing Regulation of Generic Drugs*, N.Eng.J.Med Volume 357:1993-1996 November 15, 2007.

[90] Michelle L. Kirsche, "As brand-generic alliances grow, opponents cry foul," Drug Store News, August 23, 2004.

[91] IMS Health*: Biosimilars: How Strong a Market?*, Sep 4, 2007, *available at* www.imshealth.com/ims/portal/front/articleC/0,2777,6599_5266_82367735,00.html

[92] Lisa Layman (Gen. Pharm. Assn, Assoc. VP of Govt. Aff. & Policy, quoted in FDA Legislative Watch (04/01/08) "Potential Federal Drug savings Could Propel Biosimilars Bill," *available at* www.fdalegislativewatch.com/2008/04/potential-feder.htm.