Biosimilarity and Interchangeability in the Biologics Price Competition and Innovation Act of 2009 and FDA's 2012 Draft Guidance for Industry

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I. INTRODUCTION

THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT (BPCIA), Congress's first authorization of a biosimilar therapeutic approval pathway, was signed into law in March 2010.¹ The BPCIA creates a two-tier regulatory pathway for abbreviated licensing of a biologic therapeutic. A biosimilar is "highly similar" to the innovator biologic that serves as the reference product, and the two have no "clinically meaningful" differences.² An interchangeable biologic must not only meet the biosimilarity standard, but also must be "expected to produce the same clinical result as the reference product in any given patient."³ The terms "biosimilar" and "interchangeable" are new in the context of biologics, and Congress has left FDA and the courts considerable latitude in defining these terms. This article evaluates alternative interpretations of "biosimilar" and "interchangeable" within the scope of the BPCIA, with an emphasis on FDA's non-binding position on this question.

Whereas abbreviated review of traditional small-molecule drugs was allowed under the Hatch-Waxman Amendments of 1984,⁴ an equivalent pathway for biologics was conspicuously absent until the BPCIA was enacted. The majority of approved therapeutics are small-molecule drugs, which often consist of fewer than 50 atoms covalently bound in a known arrangement. Biologics occupy the upper end of the complexity scale and are exemplified by recombinant therapeutic proteins.^{5,6} The structure of a recombinant protein is described not only by its amino acid sequence, but by additional chemical modification, such as glycosylation, phosphorylation, acetylation, and disulfide bonds.⁷ Additional complexity arises because every amino acid chain folds into a complex three-dimensional structure that is partially—but not completely—determined by the underlying amino acid sequence.⁸ To further complicate matters, these structural attributes need not be identical in every protein within a given sample.⁹ For these reasons, a re-

combinant protein is a vastly more complex specimen than a small-molecule drug.

Despite the challenges associated with complex biologics, biotechnology and pharmaceutical companies have brought a number of important biologics to market in recent years. In 2011 in the U.S., 23% of spending on therapeutics went toward biologics.¹⁰ Although biologics and molecular entities each span a considerable price scale, a rough estimate places biologics at twenty-fold more expensive to the patient than molecular entity drugs.¹¹ In 2011, six new Biologic License

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¹Krista Hessler Carver et al. An unofficial legislative history of the Biologics Price Competition and Innovation Act of 2009. 65 Food & Drug L.J. 671, 671 (2010).

²42 USC §262(k)(2)(A) (2010).

³42 USC §262(k)(4)(A) (2010).

⁴21 USC §355(j) and 355(b)(2).

⁵U.S. Food and Drug Administration, What Are "Biologics": Questions and Answers, Apr. 30, 2009; available at www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm

⁶Parker Tresemer. Interests in the balance: FDA regulations under the Biologics Price Competition and Innovation Act. 16 UCLA J. L. & Tech. i, 4 (2012).

⁷Dr. Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, testimony before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007; available at www.fda.gov/NewsEvents/Testimony/ucm154017.htm

⁸*Id.*

⁹Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf, 10 (2012).

¹⁰IMS Institute for Healthcare Informatics: The Use of Medicines in the United States: Review of 2011, Apr 3, 2012; available at www.imshealth.com/portal/site/ims/menuitem.856807fe5773bfb9ec895c973208c22a/?vgnextoid=5687ce9e0a99f210VgnVCM10000071812ca2RCRD&vgnnextfmt=default

¹¹Tresemer, *op. cit.* n. 6 at 5.

Applications (BLAs) were approved.¹² Because of the efficacy and profitability of biologics, the number of biologics brought to market seems likely to increase.

II. BIOLOGICS PRICE COMPETITION AND INNOVATION ACT IN CONTEXT

A. An Overview of the BPCIA

The heart of the BPCIA is the introduction of an abbreviated pathway for licensure of biosimilar therapeutics.¹³ This pathway, with its relaxed structural identity requirements, is not available for small-molecule drugs. The BPCIA distinguishes between biologics and small-molecule drugs with an amended definition of the term “biologic”:

A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), 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.¹⁴ (added text is underlined)

Although complex recombinant protein therapeutics had already been considered biologics within the “analogous product” category, this definition formalizes their inclusion in the class.^{15,16} Within the category of recombinant proteins fall some of the most common new biologics, including monoclonal antibodies.¹⁷

The statute lays out five main requirements that a follow-on biologic must meet to obtain approval. First, to qualify for the abbreviated pathway, the biologic must be “biosimilar to a reference product,” where the reference product is a biologic previously licensed by FDA.¹⁸ “Biosimilar” denotes that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,”¹⁹ and that there must also be “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”²⁰ This definition explicitly recognizes that perfect identity between the follow-on biologic and the reference product is not required. Whether the follow-on biologic is biosimilar is determined using three sources of data: “analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” “animal studies (including the assessment of toxicity),” and “a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharma-

codynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.”²¹ These requirements, at first blush, sound as onerous as licensure of a new biologic. Not so; under the BPCIA, FDA may determine that an analytical study, animal study, or clinical study is unnecessary.²² Second, the statute requires that “the biological product and reference product utilize the same mechanism or mechanisms of action,” with the caveat that this property need not be addressed if the reference product’s mechanism of action is unknown.²³ Third, the BPCIA requires that “the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product.”²⁴ Fourth, the “route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product.”²⁵ The second through fourth requirements call for identity, in contrast to the biosimilarity requirement. A fifth requirement is that the manufacturing facility meet standards designed to assure safety, purity, and potency.²⁶ A follow-on biologic meeting these five requirements will be approved as biosimilar to the reference product.

The BPCIA is particularly favorable to sponsors who demonstrate extremely close identity between the biosimilar and the reference product. This type of biologic is called an “interchangeable” biologic.²⁷ A biologic is interchangeable if it meets the biosimilarity requirements and fulfills two additional criteria.²⁸ First, there is a clinical efficacy hurdle to clear: the biologic must “be expected to produce the

¹²CDER Drug and Biologic Calendar Year Approvals as of December 31, 2011; available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM276984.pdf

¹³42 USC §262(k).

¹⁴42 USC §262(i)(1).

¹⁵CBER/CDER Intercenter Agreement, Oct. 1991; available at www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm

¹⁶Stroud, 63 ADMLR 599 (2011) at 622.

¹⁷*Id.*

¹⁸42 USC §262(k)(2)(A)(i)(I).

¹⁹42 USC §262(i)(1).

²⁰*Id.*

²¹42 USC §262(k)(2)(A)(i)(I)(aa)–(cc).

²²42 USC §262(k)(2)(A)(ii).

²³42 USC §262(k)(2)(A)(i)(III).

²⁴42 USC §262(k)(2)(A)(i)(III).

²⁵42 USC §262(k)(2)(A)(i)(IV).

²⁶42 USC §262(k)(2)(A)(i)(V).

²⁷42 USC §262(k)(3)(A).

²⁸42 USC §262(k)(4).

same clinical result as the reference product in any given patient.”²⁹ Second, it must be safe for a patient to switch between the reference product and the follow-on biologic.³⁰ In particular, if the biologic is a product that is administered more than once to an individual, “the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”³¹

Significant rewards await the sponsor who demonstrates interchangeability. The first interchangeable biological product receives up to one year of exclusivity over subsequent follow-on biologics.³² A temporary duopoly will preserve high prices, increasing the profitability of the follow-on biologic. The interchangeable biologic also enjoys an advantage over the brand-name equivalent, because pharmacies will be free to substitute the interchangeable biologic without consulting the prescribing health care provider.³³ This freedom to substitute makes it unnecessary for the follow-on biologic’s seller to build name recognition among doctors.

B. Comparison of the Biosimilar Approval Pathway with the Generic Small-Molecule Drug Approval Pathway

The most analogous U.S. law to the BPCIA is the approval scheme for generic small-molecule drugs. The Hatch-Waxman Amendment of 1984 defines two expedited pathways, the Abbreviated New Drug Application (ANDA) and the 505(b)(2) “paper NDA” pathway.³⁴ Hatch-Waxman has been astoundingly successful in ushering generic drugs into the market. Just before its enactment, generic drugs occupied a 19% share of all prescriptions.^{35,36} By 2007, that share had risen to 67% of all prescriptions.³⁷ Generics’ increase in market share is accompanied by lower prices, with generic drugs selling for anywhere between 5% and 79% of the brand-name drug’s price one year after entry.³⁸

Under the Hatch-Waxman approval process, the sponsor of a generic drug must show that its drug is “bioequivalent” to the reference drug.^{39,40} The sponsor of a new molecular entity and the sponsor of the generic equivalent must both show data relating to chemistry, manufacturing, quality controls, labeling, and testing.^{41,42} However, only the innovator must provide data from animal, clinical, and bioavailability studies.⁴³ The generic sponsor must instead show only bioequivalence to the reference drug.⁴⁴

Bioequivalence of a molecular entity is akin to biosimilarity in a follow-on biologic, although distinctions exist. The data required to show biosimilarity may be much more extensive than the data sufficient for approval of a generic molecular entity.⁴⁵ Whereas a generic sponsor need not present animal studies and

clinical studies, a biosimilar sponsor can omit them only at the discretion of FDA.⁴⁶ The sponsor of a biosimilar must show that it operates by the same mechanism as the reference product, assuming one is known⁴⁷; a generic molecular entity sponsor need not.^{48,49}

The Hatch-Waxman approval pathway strictly requires that the generic drug be the same molecule as the innovator drug. The state of technology allows sponsors to show identity quite easily. In contrast, the BPCIA has a more relaxed requirement for showing that the follow-on biologic is structurally similar to the reference product, acknowledging both that the state of technology may not allow us to confidently show identity, and also that in a complex macromolecule, some small structural changes may have no clinical effect. In terms of drug function, the pathways’ stringencies are reversed. The sponsor of a generic small-molecule drug need not do even one animal experiment or clinical trial. In contrast, the biosimilar sponsor may need to perform both.

Although Hatch-Waxman and the BPCIA provide distinct approval pathways, therapeutics do not fall so neatly into two classes. Some therapeutics (such as aspirin, a mere 21 atoms⁵⁰) are unambiguously small-molecule drugs. Others (such as Herceptin, made up of thousands of atoms and produced in cul-

²⁹42 USC §262(k)(4)(A)(ii).

³⁰42 USC §262(k)(4)(B).

³¹*Id.*

³²42 USC §262(k)(6).

³³42 USC §262(i)(3).

³⁴21 USC §§355(j) and 355(b)(2).

³⁵Pharmaceutical Research and Manufacturers of America letter to FTC re Evolving IP Marketplace – Comment, Project No. P09300 (2009) at 3; available at <http://ftc.gov/os/comments/iphearings/540872-00030.pdf>

³⁶Tresemmer, *op. cit.* n. 6 at 7.

³⁷*Id.*

³⁸Henry Grabowski *et al.* Entry and competition in generic biologics. *Manage. Decis. Econ.* 28:439, 444 (2007).

³⁹21 USC §355(j)(2)(A)(iv).

⁴⁰Stroud, *op. cit.*, n. 16 at 622.

⁴¹21 USC §355(j)(3)(G), 21 USC §355(j)(2)(a)(i), and 21 USC §355(j)(2)(a)(ii)(regarding the ANDA process), 21 USC §355(b)(1) (regarding the NDA process).

⁴²Stroud, *op. cit.*, n. 16 at 623.

⁴³*Id.*

⁴⁴*Id.* at 624.

⁴⁵*Id.*

⁴⁶42 USC §262(k)(2)(A)(ii).

⁴⁷42 USC §262(k)(2)(A)(i)(II).

⁴⁸*See* 21 USC §355.

⁴⁹Stroud, *op. cit.*, n. 16 at 625.

⁵⁰Aspirin Comprehensive Prescribing Information; available at www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201-Professional%20Labeling.pdf

tured mammalian cells⁵¹) are clearly biologics. There is, however, a gray area between the two categories. The BPCIA draws a border through the gray area.

Per the BPCIA, a biologic includes “a protein (except any chemically synthesized polypeptide).”⁵² A quick reading might suggest that the distinction is the method of manufacture: a protein is a small-molecule drug if it is chemically synthesized and a biologic if it is made by any other method, including recombinant production in living cells. FDA views this reading as overly simplistic.⁵³ In view of Congress’s choice to use two partially overlapping terms, “protein” and “polypeptide,” FDA sees an amino acid length requirement in the statute.⁵⁴ Specifically, FDA interprets “protein” as a polymer greater than 40 amino acids in length and “polypeptide” as a polymer less than 100 amino acids in length.⁵⁵ Thus, under FDA’s definition, a protein that is synthesized chemically and is 100 amino acids in length would be regulated as a biologic even if it never came near a living cell. Furthermore, although amino acid length might seem to be a physical property not subject to dispute, FDA has adopted a flexible definition of length. With respect to polypeptides, FDA states “[c]hemically synthesized compounds greater than 99 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.”⁵⁶ A similar provision applies to proteins.⁵⁷ Thus, it appears that certain amino acids will not count toward the length of the polypeptide if FDA deems them unimportant. This interpretation may be intended to allow manufacturers to add protein tags to the basic therapeutic protein without stepping over the length limitations. A tag is an amino acid sequence added to the protein—for example, to facilitate purification during manufacturing process. Recognizing the complexity of the regulations, FDA encourages prospective sponsors to contact FDA to discuss the categorization of the therapeutic.⁵⁸

Given the high stakes, it seems likely that sponsors of innovator therapeutics will try to strategically classify gray-area therapeutics to maximize their protection. In particular, an innovator will probably prefer to have its therapeutic licensed as a biologic, so that follow-on competitors will have to satisfy the rigorous biosimilar approval pathway. Compounding this motivation, the biosimilar pathway is an even more attractive choice for innovators because it confers a 12-year period of regulatory exclusivity,⁵⁹ compared with as long as five years under Hatch-Waxman approval.⁶⁰

The distinction between drugs and biologics is further muddled by historical factors. FDA has historically treated insulin, one of the earliest therapeutic peptides, as a drug, not a biologic.^{61,62} In 1941, despite the fact that therapeutic insulin was produced from animal tissue, Congress placed insulin within the domain of the FDC

Act, not the PHS Act which governed natural source biological products.^{63,64} Later, in 1982, when recombinant insulin was brought to market, it was also regulated under the FDC Act.^{65,66} Insulin is a relatively small peptide containing 51 amino acids (specifically, a 21-amino acid chain and a 30-amino acid chain covalently linked).⁶⁷ When sponsors presented other short proteins for approval—including glucagon, human growth hormone, hormones to treat infertility, hormones used to manage menopause and osteoporosis, and even some enzymes (hyaluronidase and urokinase)—FDA also regulated them as drugs rather than as biologics.⁶⁸ Some of these products seem to be biologics according to FDA’s interpretation of the BPCIA definition. For example, Genotropin (a human growth hormone therapeutic) is 191 amino acids in length and is produced recombinantly in bacterial cells.⁶⁹ Nevertheless, for the time being, these biologics are regulated under the Hatch-Waxman Act, together with small molecule drugs, so generic manufacturers can gain approval without the heightened testing requirements imposed by the BPCIA. For instance, the 505(b)(2) process was used to approve Omnitrope, a follow-on human growth hormone.⁷⁰

⁵¹Roche package insert for Herceptin; available at www.roche-australia.com/fmfiles/re7229005/downloads/oncology/herceptin-pi.pdf

⁵²42 USC §262(i)(1).

⁵³Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf, 12 (2012).

⁵⁴*Id.*

⁵⁵*Id.* at 13.

⁵⁶*Id.*

⁵⁷*Id.*

⁵⁸*Id.*

⁵⁹42 USC §262(k)(7)(A).

⁶⁰21 USC §§355(c)(3)(E)(ii).

⁶¹21 USC §356.

⁶²Judith Johnson, FDA Regulation of Follow-On Biologics, Congressional Research Service, 1, 6 (2010).

⁶³21 USC §356.

⁶⁴Johnson, *op. cit.*, n. 62 at 6.

⁶⁵*Id.*

⁶⁶See also Frederic J. Geissel, The U.S. Food and Drug regulatory process: administrative aspects of certification of insulins, in *Insulins, Growth Hormones and Recombinant DNA Technology* 201 (John L. Gueriguian *et al.*, eds., 1981).

⁶⁷Package insert for NOVOLIN® human insulin; available at <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=10574>

⁶⁸Johnson, *op. cit.*, n. 62 at 7.

⁶⁹Genotropin prescribing information; available at <http://medicaidprovider.hhs.mt.gov/pdf/genotropinrxinformation.pdf>, 7 (2008).

⁷⁰The FDA response to citizen petition of Pfizer *et al.* (May 30, 2006) 1; available at www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf

This historical inconsistency will be straightened out under the BPCIA's new definition of biologics, and many of the proteins currently classified as drugs will be recognized as biologics. To ease the transition, the BPCIA includes a grace period.⁷¹ For a period of 10 years after the BPCIA's enactment, a biologic that would otherwise be subject to the BPCIA may instead use the Hatch-Waxman process under Section 505 of the FDCA, if the biologic belongs to a product class containing at least one product that was approved prior to enactment.⁷² After 10 years, any biological product approved under the Hatch-Waxman process will be deemed a biologic licensed under the BPCIA.⁷³ Under the grace period provision, follow-on peptides such as human growth hormone can continue to use Hatch-Waxman approval for 10 years. After that point, new applications for approval of biologics will be subject to the more rigorous biosimilarity requirements.

The number of therapeutics eligible for this transition provision depends on the definition of "product class." FDA has adopted a fairly broad definition, consistent with Congress's goal of promoting follow-on biologics.⁷⁴ To be part of a product class, a follow-on biologic need only be homologous (similar in amino acid sequence) to the natural gene to which the innovator biologic is homologous.⁷⁵ In addition to structural changes being permissible, functional differences are also allowed. Two biologics may fall into the same product class even if they exhibit different pharmacokinetic properties (the speed at which the therapeutic is absorbed, distributed, metabolized, and excreted from the body).⁷⁶ If the innovator biologic is not homologous to any naturally occurring gene, it is in the same class as a follow-on biologic if the two share a biological activity.⁷⁷ In this scenario, FDA does not seem to require any structural homology between the innovator biologic and the follow-on biologic. Thus, FDA interprets the BPCIA to provide a generous transition period for biologics of a type historically categorized as drugs. The grace period may prompt follow-on sponsors to rush eligible follow-on biologics into the regulatory process while the Hatch-Waxman pathways are still available to them.

It is worth pausing to appreciate that, like the BPCIA, Hatch-Waxman creates two tiers of similarity. FDA maintains the Orange Book (formally, the Approved Drug Products with Therapeutic Equivalence Evaluations) and gives drugs an equivalence rating of A or B.^{78,79} A B rating signifies bioequivalence, and an A rating signifies bioequivalence and interchangeability.^{80,81} As with interchangeable biologics, a pharmacist may substitute an interchangeable generic without a doctor's permission.⁸²

C. Comparison of U.S. Biosimilar Approval Pathway with Foreign Pathways

The U.S. is not the first country to establish an abbreviated pathway for biosimilar approval: Canada

and Europe have done the same.⁸³ This section provides a brief description of foreign biosimilar approval frameworks and a comparison with the BPCIA.

The European Medicines Agency, which grants regulatory approval to biologics in the European Union, implemented an abbreviated approval pathway for follow-on biologics in 2004.⁸⁴ As of 2011, at least 14 biosimilars have been approved in the European Union.⁸⁵ As under the BPCIA, in Europe, a sponsor must show the follow-on biologic has a structure similar to that of the reference product.⁸⁶ Although some structural differences are allowed, structural differences generally call for functional and clinical testing.⁸⁷ Human trials may—in theory—be unnecessary to gain approval, but in practice, most follow-on biologics show at least some small differences from the innovator biologic, so comparative clinical trials are required for most European biosimilar applications.^{88,89} The clinical trials are not as extensive as those for a new biologic, though.⁹⁰ It remains to be seen whether FDA will waive the requirement for clinical trials often enough to make the U.S. approval pathway less demanding than that in Europe.

In Canada, unlike Europe and the U.S., the regulatory agency (HealthCanada) took the position that no new legislation was needed to allow abbreviated approval of biosimilars.⁹¹ To gain approval, the follow-on biologic must have demonstrated similarity to a reference product.⁹² As in the U.S., identity is not required.⁹³ In

⁷¹Pub. L. 111-148, title VII, §7002(e)(2)(A) Mar. 23, 2010, 124 Stat. 817.

⁷²*Id.* at §7002(e)(2)(B).

⁷³*Id.* at §7002(e)(4).

⁷⁴Guidance for Industry: Biosimilars, *op. cit.*, n. 53 at 14.

⁷⁵*Id.*

⁷⁶*Id.*

⁷⁷*Id.*

⁷⁸Richard R. Abood, *Pharmacy Practice and the Law* 140 (6th ed. 2011).

⁷⁹Stroud, *op. cit.*, n. 16 at 622.

⁸⁰Abood, *op. cit.*, n. 78 at 141.

⁸¹Stroud, *op. cit.*, n. 16 at 622.

⁸²*Id.*

⁸³Noel Courage and Ainslie Parsons, The comparability conundrum: biosimilars in the United States, Europe and Canada, 66 Food & Drug L.J. 203, 209 (2011).

⁸⁴*Id.*

⁸⁵*Id.* at 211.

⁸⁶*Id.* at 210.

⁸⁷*Id.*

⁸⁸EMA, *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues* (CHMP/BMWP/42832/2005), effective Jun. 1, 2006, at 6.

⁸⁹Courage and Parsons, *op. cit.*, n. 83 at 210.

⁹⁰*Id.*

⁹¹*Id.* at 212.

⁹²*Id.*

⁹³*Id.* at 213.

Canada, clinical studies are required.⁹⁴ HealthCanada requires not only pharmacokinetic and pharmacodynamic⁹⁵ studies in humans, but also comparative clinical trials.⁹⁶ Only one follow-on biologic (Omnitrope) has been approved in Canada as of 2011.⁹⁷

III. WHAT IS BIOSIMILARITY?

A. Statutory Definition of “Biosimilar” and Competing Interpretations

For a biosimilar therapeutic to gain approval, it must satisfy the definition of “biosimilar” set out in the BPCIA, as refined by FDA and, eventually, the courts. Because the BPCIA is in its infancy, it is far from settled how “biosimilar” ultimately will be interpreted.

By statute, a biosimilar is highly similar to the reference product (notwithstanding minor differences in clinically inactive components) and has no clinically meaningful differences in safety, purity, and potency from the reference product.⁹⁸ The statute’s use of relative language (“highly similar,” “minor,” “clinically meaningful”) leaves FDA and the courts considerable latitude to construe the terms. In keeping with the flexible standard evident from the statutory text, FDA intends to consider the totality of the evidence provided by a sponsor to show that a product is biosimilar.⁹⁹ A totality of the evidence standard is not new to FDA; it is already used to determine whether an innovator drug is clinically effective.¹⁰⁰

A flexible approach is not unjustified. Because the number of biologics approved each year is in the single digits,¹⁰¹ a flexible approach should not be unduly burdensome on FDA. In addition, because biologics range from the slightly complex to the extremely complex, a flexible approach allows FDA to tailor the requirements accordingly. On the other hand, one challenge always inherent in a flexible standard is how to ensure that the standard will be applied fairly and uniformly. In another area of law, Justice Scalia described “th’ ol’ ‘totality of the circumstances’ test” as “that test most beloved by a court unwilling to be held to rules (and most feared by litigants who want to know what to expect).”¹⁰² FDA can reduce uncertainty by producing and adhering to detailed guidance documents for each class of product, as is done in Europe.^{103,104} The BPCIA permits the Secretary to issue guidance with respect to licensing of follow-on biologics.¹⁰⁵

Interpreting the statutory definition of “biosimilar” requires the interpretation of several key terms. First, it remains an open question exactly how FDA and the courts will interpret the language of “highly similar” to a reference product. It is clear, at least, that differences between the follow-on biologic and the reference product are permitted with respect to both the active agent and the inactive components. Congress’s choice of the term “biosimilar” clearly denotes that

the follow-on active substance need not be identical to the innovator product. Tolerance for structural differences is also apparent in the statute’s provision that a biosimilar should be “highly similar” to the reference product.¹⁰⁶ At the current state of technology, it is all but impossible for two companies to manufacture perfectly identical biologics,¹⁰⁷ especially when the innovator maintains manufacturing details as trade secrets. The statute also allows “minor differences in clinically inactive components.”¹⁰⁸

Turning now to the second prong of the definition, the key question seems to be how FDA and the courts will interpret “clinically meaningful differences.” Without offering a comprehensive definition, FDA suggests that the term could “include a difference in the expected range of safety, purity, and potency of the proposed and reference products.”¹⁰⁹ Clearly, more detail will be needed. Will a 1% decrease in *in vitro* activity be dispositive? A 50% decrease? Will an increase in adverse reactions be looked on more harshly than a decrease in efficacy? What kinds of impurities are the most important? Several factors will likely play into the decision. With respect to safety, we should consider the frequency and severity of side effects, the willingness of patients to tolerate adverse reactions (*e.g.*, greater in more serious diseases), and the ability to detect and treat adverse reactions promptly. Regarding potency, we should consider the degree of decreased activity, the ability to

⁹⁴*Id.*

⁹⁵Pharmacodynamics is the study of how the therapeutic affects the patient. Pharmacodynamic studies include whether the drug binds to a particular target or alters the amount of a particular protein.

⁹⁶Courage and Parsons, *op. cit.*, n. 83 at 213.

⁹⁷*Id.* at 212.

⁹⁸42 USC §262(i)(1).

⁹⁹Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; *available at* www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf, 2 (2012).

¹⁰⁰*Id.*

¹⁰¹CDER Drug and Biologic Calendar Year Approvals as of December 31, 2011; *available at* www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM276984.pdf

¹⁰²*U.S. v. Mead*, 533 U.S. 218, 241 (2001).

¹⁰³Courage and Parsons, *op. cit.*, n. 83 at 209.

¹⁰⁴See also EMEA, *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues* (CHMP/BMWP/42832/2005), effective Jun. 1, 2006.

¹⁰⁵42 USC §262(k)(8).

¹⁰⁶42 USC §262(i)(2)(A).

¹⁰⁷Woodcock, *op. cit.* n. 7.

¹⁰⁸42 USC §262(i)(2)(A).

¹⁰⁹Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, 99 at 8.

compensate for decreased activity by administering a higher dose or changing the formulation, and the danger of accidentally administering too low a dose to the patient (*e.g.*, in life-threatening diseases, or in infections where a low dose could breed resistant pathogens). As to purity, we should give greater attention to impurities thought to cause adverse reactions based on clinical or laboratory studies, and less weight to impurities thought to be safe according to clinical or laboratory studies.

The statutory terms “safety, purity, and potency” have well-established meanings in the context of drug approval. Briefly, *safety* refers to relative freedom from harmful effect, taking the patient’s condition at the time of administration into account.¹¹⁰ *Potency* refers to the therapeutic effectiveness of the drug.¹¹¹ *Purity* refers to the absence of contaminants, whether harmful or not.¹¹²

It is clear that the statutory definition of biosimilarity leaves much room for interpretation. To supplement this definition, the statute describes several sources of evidence that sponsors can use to demonstrate biosimilarity.

B. Statutory Requirements for Demonstrating Biosimilarity and Competing Interpretations

In contrast to the vague definition of biosimilar, the statute provides considerable clarity as to the data required to demonstrate biosimilarity: analytical, animal (including toxicity), and clinical (including immunogenicity and pharmacokinetics or pharmacodynamics).¹¹³ Uncertainty is reintroduced by the fact that FDA may determine that an analytical, animal, or clinical study is unnecessary.¹¹⁴

FDA takes the position that the requirements for demonstrating biosimilarity should use a stepwise approach.¹¹⁵ This approach would call for a sponsor to begin with *in vitro* experiments, which are the simplest and least expensive studies.¹¹⁶ The number and scale of animal and human studies required will depend on the results of the earlier studies.¹¹⁷ FDA will then weigh the available studies using the totality-of-the-evidence standard.¹¹⁸

FDA guidance documents spell out the stepwise approach in more detail. The first step is structural and functional characterization of the biologic.¹¹⁹ The more similar the follow-on biologic appears to be to the innovator biologic based on *in vitro* studies, the more likely it is that animal and clinical testing can be minimized.¹²⁰ FDA guidance is agnostic as to whether the structural differences are intentional. For instance, the guidance states that addition or removal of amino acids at either end of the biosimilar relative to the reference product is unlikely to affect its potency.¹²¹ These amino acid sequence differences can generally be avoided by careful construction of the recombinant DNA sequence. The

industry group BIO, on the other hand, recommends that FDA not permit intentional differences to amino acid sequence and formulation if these differences can be reasonably avoided.¹²² In support of its position, FDA might argue that the import of a structural change in a biologic is its effect on therapeutic function, not the state of mind of the scientist producing it. On the other hand, BIO might argue that because any structural differences between biologics might affect their function, follow-on sponsors should eschew intentional differences.

The next step to consider is animal testing. There are two main types of tests on animals: efficacy and toxicity. Toxicity tests are the most likely to be required. FDA considers animal toxicity data useful when structural and functional characterization do not provide certainty that the product will be safe in humans.¹²³ This probably will be the case for every biologic, because it is difficult or impossible to test for every possible contaminant and to predict adverse effects of the active ingredient on every tissue and organ using only *in vitro* tests. FDA typically will require only general toxicity studies; specific tests for reproductive toxicity, developmental toxicity, and carcinogenicity will not be required if the reference product did not appear to have those properties.¹²⁴

¹¹⁰21 CFR §600.3(p), providing “The word ‘safety’ means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.”

¹¹¹21 CFR §600.3(s), providing “The word ‘potency’ is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.”

¹¹²21 CFR §600.3(r), providing “‘Purity’ means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.”

¹¹³42 USC §262(k)(2)(A)(i)(I)(aa)–(cc).

¹¹⁴42 USC §262(k)(2)(A)(ii).

¹¹⁵Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 2.

¹¹⁶*Id.* at 7.

¹¹⁷*Id.* at 12.

¹¹⁸*Id.* at 2.

¹¹⁹*Id.* at 7.

¹²⁰*Id.*

¹²¹*Id.* at 9.

¹²²BIO Comments on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; available at www.bio.org/sites/default/files/2012-04-16%20Scientific%20Considerations%20-%20FINAL.pdf, 9 (April 16, 2012).

¹²³Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 11.

¹²⁴*Id.*

Animal efficacy studies are unlikely to be required, especially if the biologics appear similar in *in vitro* tests. Animal pharmacokinetic and pharmacodynamic studies will likely be uncommon in the licensing process because FDA does not require them and will not accept them as a substitute for the same studies performed on humans.¹²⁵

The next step is human testing. FDA recommends that sponsors perform human pharmacokinetic and pharmacodynamic studies to show that the follow-on and innovator products reach the necessary concentrations in the appropriate regions of the body.¹²⁶ FDA recommends a 5-day study for biologics that break down quickly.¹²⁷ A second key study highlighted by FDA is an immunogenicity assessment in human subjects.¹²⁸ This provision probably reacts to the concern that it is difficult to predict whether a given biologic will produce an inappropriate immune response in a patient, because *in vitro* and animal studies are poorly predictive of the likelihood of such a reaction.¹²⁹ Immunogenicity is of greater concern with biologics than small-molecule drugs, because the immune system is geared to raise a response to a foreign protein more than to a small molecule.¹³⁰ The risk is heightened when biologics are produced in non-human mammalian cells, because trace proteins from these cells—or non-human patterns of chemical modification to the biologic—can trigger an unwanted immune response. Immunogenicity is not only a safety concern, but an efficacy concern, because neutralizing antibodies can block the effectiveness of a therapeutic.¹³¹ FDA specifies that a sponsor should conduct a 1-year immunogenicity study in human patients to gain approval for a chronically administered biologic.¹³² The time and expense of an immunogenicity study stands in contrast with the recommended five-day course of a pharmacokinetic study. Clearly, adverse immune reactions are at the forefront of FDA's attention.

Clinical trials showing efficacy in humans are the most expensive type of study and the type most likely to be waived at least in part. FDA identifies five factors that determine the extent of clinical trials necessary: (1) the similarity of the follow-on biologic to its reference product in terms of structure and *in vitro* function; (2) the extent to which structural and functional differences predict clinical efficacy; (3) the extent to which human pharmacokinetic and pharmacodynamic studies predict clinical efficacy; (4) the track record of the reference product and related biologics, including post-market studies; and (5) clinical experiences with the proposed product, for instance, outside the U.S.¹³³ If the sponsor performs clinical trials, FDA will license the follow-on biologic only if it is no worse—and no better—than the reference product.¹³⁴ FDA is concerned that greater efficacy will correlate with increased adverse effects.¹³⁵ If the biologic is truly more effective than the reference product, FDA may

still license it, but as a new biologic that does not rely on a reference product.¹³⁶

It remains to be seen how often FDA will waive clinical trials for biosimilars. The statute calls for clinical testing unless FDA determines it is unnecessary.¹³⁷ This language suggests a presumption that clinical testing is necessary; this presumption can be overcome by evidence, such as a showing that the reference and follow-on biologic are structurally similar.¹³⁸ However, FDA's interpretation also could be understood to mean that clinical testing is a "residual requirement, and triggered only if there are gaps or insufficiencies" in the pre-clinical data.¹³⁹ One suggestion of FDA's stance on this issue comes from the recent approval of a generic version of Lovenox (enoxaparin).¹⁴⁰ Enoxaparin is a complex carbohydrate drug composed of low-molecular-weight heparin.^{141,142} FDA approved a generic version via the ANDA pathway.^{143,144} FDA did not require clinical trials for safety or efficacy despite the drug's complexity.¹⁴⁵ Dr. Rachel Behrman, a senior FDA official, cited the Lovenox approval as an example of how FDA would approach licensing of a biosimilar.^{146,147} She contrasted the Lovenox approval with Europe's biosimilar

¹²⁵*Id.* at 12.

¹²⁶*Id.* at 7.

¹²⁷*Id.* at 18.

¹²⁸*Id.* at 14.

¹²⁹*Id.* at 12.

¹³⁰Letter of Frank M. Torti, M.D., M.P.H., to Rep. Pallone, Chairman, Subcomm. on Health, H. Comm. on Energy & Commerce (Sept. 18, 2008) at 1; available at http://step.berkeley.edu/Journal_Club/paper2_110309.pdf

¹³¹Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 14.

¹³²*Id.* at 15.

¹³³*Id.* at 16.

¹³⁴*Id.*

¹³⁵*Id.*

¹³⁶*Id.*

¹³⁷42 USC §262(k)(2)(A)(ii).

¹³⁸BIO Comments, *op. cit.*, n. 122 at 4.

¹³⁹*Id.*

¹⁴⁰Stroud, *op. cit.*, n. 16 at 625.

¹⁴¹Lovenox prescribing information; available at <http://products.sanofi.us/lovenox/lovenox.html>

¹⁴²Stroud, *supra* at n. 167.

¹⁴³FDA Letter to Aventis Pharmaceuticals, Inc., July 23, 2010, FDA Docket No. FDA-2003-P-0273, 1; available at www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafety/InformationforPatientsandProviders/UCM220083.pdf

¹⁴⁴Stroud, *supra* at 625.

¹⁴⁵FDA Letter to Aventis Pharmaceuticals, Inc., *supra* at 2; Stroud, *supra* at 625.

¹⁴⁶Udwin, "Biosimilars two-step" BioCentury, May 9, 2011; available at www.biocentury.com/biotech-pharma-news/coverstory/2011-05-09/primer-on-how-fda-plans-to-review-biosimilars-for-similarity-interchangeability-a1

¹⁴⁷Stroud, *supra* at n. 169.

approval pathway, which generally requires clinical trials.¹⁴⁸ Perhaps FDA is prepared to waive clinical efficacy studies for the majority of follow-on biologics. BIO takes the opposite position, stating that clinical trials for efficacy will be necessary for most follow-on biologics.¹⁴⁹

With respect to the stepwise approach, the FDA guidance does not specify what kind of structural differences will call for additional animal or clinical studies. Is a missing amino acid better or worse than a missing chemical modification? Is a conformational change more or less worrisome than an aberrant functional study? These questions should be answered on a case-by-case basis with reference to the scientific literature. If a peer-reviewed scientific article shows that a particular structural change has no detectable effect on a protein's function, that structural change should not mandate animal or human studies. FDA plans to consider structural differences in light of general knowledge of molecular biology. For instance, it is generally accepted that amino acids added to or removed from either end of a protein are less likely to affect its function than amino acids added to or removed from functional domains within the protein. Accordingly, FDA expects that amino acids added or removed at the ends of the protein will not usually call for animal or clinical testing.¹⁵⁰

The BPCIA does not specify whether it is more damaging for a sponsor to present unfavorable structural or functional data, or to simply not do the experiment that yields those data. For instance, would FDA be more likely to request clinical trials if the sponsor presented nine experiments all showing the follow-on biologic is structurally similar, or ten experiments, nine of which showed structural similarity and one of which showed a difference? The risk of penalizing unfavorable data is that sponsors will be unwilling to do thorough testing, because every additional test becomes a potential point of failure. This is clearly an undesirable outcome; as a matter of public safety, we should encourage extensive testing. Perhaps in reaction to this concern, FDA encourages comprehensive analysis, stating, "[t]he more comprehensive and robust the comparative structural and functional characterization are, the stronger the scientific justification for a selective and targeted approach to animal and/or clinical testing."¹⁵¹

The requirements for demonstrating biosimilarity will, in general, be more extensive than those for a single manufacturer to show that a change to its manufacturing process did not affect its product.¹⁵² FDA's rationale is that a manufacturer that modifies its own manufacturing process has extensive knowledge about the product, including the identity of each intermediate in the manufacturing process and the acceptable bounds within which key parameters can differ.¹⁵³ A competitor producing a follow-on biologic, in contrast, will not only use a different

manufacturing plant and process, but will likely start with a different cell line and DNA sequence encoding the biologic.¹⁵⁴ These factors indicate that the structural differences between an innovator and a follow-on biologic are likely greater than those between a biologic before and after a manufacturing change. There is accordingly a greater burden of proof to show that a follow-on biologic is similar to an innovator biologic.

By statute, the reference drug against which a sponsor compares its biosimilar must be an FDA-licensed biologic.¹⁵⁵ FDA offers some flexibility around this requirement. While the key comparative studies should focus on the previously FDA-licensed biologic, a sponsor may provide supplemental data comparing the follow-on biologic with a reference product that is not licensed in the US to help fulfill the biosimilarity requirements.¹⁵⁶ In particular, FDA requires that the analytical studies and at least one clinical pharmacokinetic study be comparisons of the follow-on biologic with the U.S. reference product.¹⁵⁷ To be able to make this limited use of a foreign comparator, the sponsor must show that the foreign biologic has an adequate "bridge" to the U.S. reference product.¹⁵⁸ To show that two products are adequately bridged, human pharmacokinetic or pharmacodynamic studies are likely to be necessary.¹⁵⁹ It is strong evidence of bridging if the U.S. and foreign products are manufactured by the same company in the same facility.¹⁶⁰ It is unclear how often sponsors will need to take advantage of the foreign comparator option. In theory, if FDA did not request a study from an innovator, FDA should not need to request that study from a follow-on sponsor to show biosimilarity. FDA's historical reluctance to rely on foreign clinical trials also suggests that sponsors will make little use of foreign comparative data in biosimilar applications.¹⁶¹

¹⁴⁸*Id.*

¹⁴⁹BIO Comments, *op. cit.*, n. 122 at 5.

¹⁵⁰Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 9.

¹⁵¹*Id.*

¹⁵²*Id.* at 5.

¹⁵³*Id.*

¹⁵⁴*Id.*

¹⁵⁵42 USC §262(i)(4).

¹⁵⁶Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 6.

¹⁵⁷Guidance for Industry: Biosimilars, *op. cit.*, n. 53 at 7.

¹⁵⁸Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 6.

¹⁵⁹Guidance for Industry: Biosimilars, *op. cit.*, n. 53 at 7.

¹⁶⁰*Id.*

¹⁶¹*See* Federal Register, Vol. 73, No. 82, Monday, April 28, 2008, Rules and Regulations, p. 22800.

Whether a particular biologic is biosimilar to a reference product will be a difficult question, and different parties will likely have conflicting views. FDA has not yet stated what parties will have a voice in determining biosimilarity. The most obvious source is the sponsor of the biologic, because the sponsor has the burden to show biosimilarity.¹⁶² A less obvious party is the sponsor of the innovator biologic. The innovator is a valuable source of expertise, because the innovator has experience making and marketing the biologic. The innovator will surely argue that its competitor be held to the highest standard, but an innovator's bias can be useful to FDA as a counterpoint to the follow-on sponsor's opposite bias. Another potential source of advice is a foreign regulatory agency that has developed standards for biosimilarity, such as the European Medicines Agency.¹⁶³ FDA has indicated some willingness to appreciate the expertise of foreign regulatory agencies, for instance, in giving more credence to studies involving foreign reference drugs if the foreign drug was manufactured in a facility "licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation [ICH] countries)."¹⁶⁴

The BPCIA's provisions and FDA's guidance on how to demonstrate biosimilarity significantly flesh out the definition of biosimilarity. However, because the class of biologics encompasses biologics with greatly different complexities and safety profiles, for treating conditions of greatly varying severity, a flexible approach is needed. By adopting a totality of the evidence approach, FDA reserves the power to weigh disparate pieces of evidence as it considers fit.

C. Statutory Limitations on the Indications for Which a Biosimilar Is Licensed

The BPCIA will approve a follow-on biologic only to treat diseases and conditions for which the reference product was approved.¹⁶⁵ In particular, the statute provides, "[a]n application submitted under this subsection shall include information demonstrating that...the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product."¹⁶⁶ The statute also provides that a sponsor can show that a follow-on biologic is biosimilar based on (among other things) "a clinical study...sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product."¹⁶⁷

The most natural interpretation of this language appears to be that a follow-on sponsor can choose to seek approval of the biosimilar for one or more indications for which the innovator biologic is approved. An alternative, innovator-favorable interpretation would

require the follow-on sponsor to seek approval for every indication for which the innovator biologic is approved, which could require additional trials.¹⁶⁸ Another alternative, more favorable to follow-on sponsors, would require FDA to approve the follow-on biologic for multiple indications even if the follow-on sponsor only presents evidence relating to one indication. An example of this last interpretation would read the BPCIA to require FDA to approve follow-on biologics "for all conditions of use for which the products have the same mechanism of action."¹⁶⁹ The first interpretation seems more consistent with the statute for three reasons. First, the two relevant portions of the statute (quoted in the previous paragraph) do not refer to a common mechanism of action as a consideration in licensing a biologic for more than one indication. Second, in the BPCIA, Congress chose not to re-use language in an earlier bill, the Amended Access to Life-Saving Medicine Act (ALSMA), which recited "[u]pon review of an application...for a biological product, the Secretary shall issue a comparable biological product license for *all conditions of use of the reference product sharing the same mechanism or mechanisms of action* for which the applicant has demonstrated comparability for a single condition of use" (emphasis added).¹⁷⁰ Third, FDA appears not to interpret BPCIA to impose a bright-line rule that all indications with a common mechanism of action will be approved together. The FDA guidance on biosimilarity explains that if the two or more indications are closely related, an applicant can extrapolate from data relating to one indication to conclude that the biosimilar will likely be effective in the related indications.¹⁷¹ Thus, if a biosimilar is licensed for one indication, FDA may—but need not—license it for related indications if the sponsor can justify the extrapolation. The extrapolation can be based on

¹⁶²E.g., Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99 at 1.

¹⁶³Courage and Parsons, *op. cit.*, n. 83 at 209.

¹⁶⁴Guidance for Industry: Biosimilars, *op. cit.*, 53 at 7.

¹⁶⁵42 USC §262(k)(2)(A)(i)(III).

¹⁶⁶*Id.*

¹⁶⁷42 USC §262(k)(2)(A)(i)(I)(cc).

¹⁶⁸Had Congress intended to require a sponsor to seek approval for all indications for which the innovator product is licensed, it could have worded 42 USC §262(k)(2)(A)(i)(I)(cc) as "sufficient to demonstrate safety, purity, and potency in *each* condition of use for which the reference product is licensed," rather than referring to "1 or more appropriate conditions."

¹⁶⁹Tresemmer, *op. cit.*, n. 6 at 50.

¹⁷⁰Amended Access to Life-Saving Medicine Act, H.R. 1038 and S. 623, Sec. 3(k)(4)(A).

¹⁷¹Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, *op. cit.*, n. 53 at 9.

studies of the mechanism of action, pharmacokinetics, and toxicity.¹⁷²

Accordingly, Congress appears to have adopted a compromise where follow-on sponsors can choose the indications for which their biologic will be licensed, and FDA is not obligated to approve the biologic for additional indications.

D. Dosage and Administration

Under the BPCIA, FDA will license a biologic only if the “route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product.”¹⁷³ These three characteristics are fairly clear-cut in comparison with structural similarity or clinical performance.

There are only a handful of routes of administration (e.g., oral, subcutaneous, intramuscular, oral inhalation, nasal inhalation, topical, etc.), and most therapeutics clearly are appropriate for one of them. Controversy thus is unlikely over whether a particular biosimilar has the same route of administration as its reference product.

A dosage form refers to the physical form in which a drug is produced.¹⁷⁴ In general, a drug’s dosage form will be unambiguous because FDA has enunciated the borders of each category. For example, FDA considers the following dosage forms to be the same “injectable” dosage form: a pre-filled syringe, an auto-injector device, and a kit containing a drug vial and a separate syringe.¹⁷⁵

The strength of a therapeutic refers in general to its potency, but there are several ways to measure potency. One simple measurement is a physical characteristic, such as milligrams of therapeutic per milliliters of liquid (mg/mL).¹⁷⁶ The disadvantage of this measurement is that it does not necessarily correlate with the effect of the therapeutic on a patient. With some biologics, the lot-to-lot variability is high, so that in different lots, a different percentage of the active ingredient becomes inactive. In a case like this, two lots may produce the same amount of biologic in mg/mL, but one lot will have a lower therapeutic activity than the other. A better measurement is units of activity (e.g., in units/mL), defined according to some relevant *in vitro* assay.¹⁷⁷ This measurement balances accuracy and ease of calculation. The gold standard measurement would be the therapeutic effect of the biologic on a patient, but calculating this measurement for each batch of a therapeutic would be prohibitively expensive and time-consuming. FDA recommends that the follow-on sponsor use the same measurement as the innovator,¹⁷⁸ presumably to facilitate comparison of the two biologics.

FDA’s recommendation seems innovator-friendly because it allows the innovator to choose the standard of comparison. If an innovator chooses mg/mL, the follow-on biologic must possess the same activity as

the innovator. If the follow-on biologic is less active than the innovator, the same concentration in mg/mL of each biologic will give a lower activity of the follow-on biologic. The follow-on manufacturer cannot simply add more of the biologic to increase the total activity, because doing so would increase the concentration (mg/mL) above that of the reference product. In contrast, a manufacturer could use this strategy if the measurement were units/mL. In sum, if an innovator chooses mg/mL, the innovator creates an extra hurdle for follow-on competitors. FDA guidance seems to motivate innovators to measure their drug by physical characteristics if possible.

IV. WHAT IS INTERCHANGEABILITY?

A. Statutory Definition of “Interchangeable” and FDA’s View of Interchangeability

The BPCIA creates an elevated tier of biosimilars, called “interchangeable” biologics, that have particularly close identity to the reference product.¹⁷⁹ An interchangeable biologic must “be expected to produce the same clinical result as the reference product in any given patient.”¹⁸⁰ In addition, it must be safe for a patient to switch brands between the innovator biologic and the interchangeable biologic. In particular, if the biologic is a product that is administered more than once to an individual, “the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”¹⁸¹

It is far too early to tell how “interchangeable” ultimately will be interpreted. Prior to the BPCIA, interchangeability was not defined by FDA.¹⁸² Although FDA has recently released a guidance document discussing the biosimilarity standard,¹⁸³ it has not yet released guidelines for interchangeability. Per FDA’s biosimilarity guidelines, FDA has not yet decided

¹⁷²*Id.*

¹⁷³42 USC §262(k)(2)(A)(i)(IV).

¹⁷⁴Drugs@FDA Glossary of Terms; available at www.fda.gov/Drugs/informationondrugs/ucm079436.htm (2012).

¹⁷⁵Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, *op. cit.*, n. 53 at 5.

¹⁷⁶*Id.* at 10.

¹⁷⁷*Id.*

¹⁷⁸*Id.* at 11.

¹⁷⁹42 USC §262(k)(3)(A).

¹⁸⁰42 USC §262(k)(4)(A)(ii).

¹⁸¹*Id.*

¹⁸²Woodcock, *op. cit.*, n. 7.

¹⁸³Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity, *op. cit.*, n. 99.

what type of information a sponsor must provide to show interchangeability.¹⁸⁴ Nevertheless, FDA has hinted that the interchangeability standard will be a rigorous one. For instance, Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research (CDER), said in 2007 that “[f]or many follow-on protein products—and in particular, the more complex proteins—there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.”^{185,186} As another example, while FDA states that it is not impossible to simultaneously show that a drug is biosimilar and interchangeable, it cautions that “it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability.”¹⁸⁷

FDA has given a few concrete indications of how the interchangeability standard will be more stringent than the biosimilarity standard. For instance, FDA plans to require an interchangeable biologic to have a delivery device and closure container very similar to those of the reference product, and non-interchangeable biosimilars will not be subject to this requirement.¹⁸⁸ Specifically, FDA may consider whether the changes alter the product’s performance or operation, or would require additional instructions from healthcare providers.¹⁸⁹ Even an alteration in the design of the device or container may raise a red flag, if it affects a critical design attribute.¹⁹⁰ As another example, FDA plans to accept (within limits) data comparing a follow-on biologic to a foreign-licensed reference product to make a determination of biosimilarity.¹⁹¹ To show interchangeability, comparison with a foreign-licensed product is likely to be insufficient.¹⁹² Judging from these examples, a sponsor will probably not clear the interchangeability hurdle by showing biosimilarity and then tacking a few additional experiments onto the application. Rather, a sponsor intending to show interchangeability should design all its biosimilarity experiments to comply with the interchangeability standard. Doing so will avoid the need to redo experiments that were sufficient for biosimilarity, but not interchangeability.

BIO, representing mostly innovators, has recommended that FDA consider 13 factors to determine whether a biologic is interchangeable with its reference product.¹⁹³ Under this framework, characteristics that weigh toward interchangeability are: (1) low complexity of the biosimilar; (2) high structural similarity between the biosimilar and reference products; (3) a known shared mechanism of action; (4) a favorable safety profile (including low immunogenicity); (5) a large window between the effective dose and a toxic dose; (6) post-marketing data show-

ing that the reference product is safe and efficacious; (7) a favorable risk-to-benefit profile; (8) a high-priority therapeutic area; (9) a similar route of administration; (10) individual characteristics of patients (patient factors) having a weak or no effect on efficacy and safety; (11) studies showing a low risk of poor results when switching between the follow-on biologic and the reference product; (12) a low rate of severe adverse events in outlier patients; and (13) a low likelihood of product drift (when innovator and follow-on products are initially similar but gradually develop differences—for instance, because of random mutations in the cell lines that produce the biologics).¹⁹⁴ Although some of these factors are familiar, factors 5, 8, 10, 12, and 13 do not appear directly drawn from the statute or FDA’s guidance on biosimilarity, and it remains to be seen whether FDA will adopt them.

FDA will allow sponsors either to request a determination of interchangeability when they file the biosimilar application, or to obtain a determination of biosimilarity first and then seek a determination of interchangeability.¹⁹⁵ If a sponsor obtains biosimilarity and interchangeability determinations in two steps, it can be important to time the two steps carefully. The sponsor will want to obtain the interchangeability determination early enough to become the first follow-on to reach the market and secure the resulting temporary exclusivity period over other follow-on manufacturers. On the other hand, performing the biosimilarity studies too early (for instance, well before the innovator’s 12-year exclusivity period is over) may be an unnecessary acceleration of expenses. If (as is likely) an interchangeability determination requires clinical trials, there may be a significant lag between the biosimilarity determination and the interchangeability determination.

¹⁸⁴Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, *op. cit.*, n. 53 at 11.

¹⁸⁵Janet Woodcock *et al.* The FDA’s assessment of follow-on protein products: A historical perspective. *Nat Rev Drug Discov* 2007;6:437, 440.

¹⁸⁶Stroud, *supra* n 178.

¹⁸⁷Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, *op. cit.*, n. 53 at 11.

¹⁸⁸*Id.* at 5.

¹⁸⁹*Id.*

¹⁹⁰*Id.*

¹⁹¹*Id.* at 8.

¹⁹²*Id.*

¹⁹³FDA Public Meeting: Approval Pathway for Biosimilar and Interchangeable Biological Products; available at www.bio.org/sites/default/files/2012-05-11-biosimilars-fda-public-hearing.pdf, 4 (May 11, 2012).

¹⁹⁴*Id.*

¹⁹⁵Guidance for Industry: Biosimilars, *op. cit.*, n. 53 at 11.

*B. Statutory Requirements
for Demonstrating Interchangeability*

FDA has not yet indicated how a follow-on sponsor can show that its biologic is “expected to produce the same clinical result as the reference product in any given patient.”¹⁹⁶ The statutory language suggests that a sponsor must perform comparative clinical trials unless a particularly predictive non-clinical test is available. Extremely predictive non-clinical tests will likely be rare as a matter of scientific difficulty and because there is little incentive to develop one. An innovator would be reluctant to develop a non-clinical test that would ease licensing of a biosimilar. A follow-on sponsor would probably not choose to develop a non-clinical test because it would need to validate the non-clinical test against a clinical trial. This expense would negate the savings of developing a non-clinical test. Thus, a clinical trial will likely be necessary to show interchangeability. FDA should provide guidance on whether a follow-on sponsor can meet this standard using a smaller or shorter clinical trial than the innovator.

The statutory reference to “any given patient”¹⁹⁷ suggests FDA will pay attention to variability identified in a clinical study. If an innovator biologic and a follow-on biologic have the same effects on average, but the innovator biologic affects all patients equally and the follow-on biologic is extremely efficacious in some patients and ineffective in others, the follow-on biologic may not be interchangeable.

FDA also has not yet stated how it will assess the risk that a patient will have an adverse reaction to switching between an innovator biologic and a follow-on biologic. One definitive way a sponsor could answer the question is to monitor efficacy and adverse effects in a clinical trial in human patients, where one group receives the reference product and the other group alternates between the reference product and the follow-on biologic. However, such a study would be expensive and time consuming, and so would negate some of the advantages of the abbreviated licensing pathway. In addition, a study of this type raises the question of whether it is ethical to switch a patient between two therapeutics, if switching is not expected to produce any benefit, and might produce an adverse event.¹⁹⁸ As an alternative, FDA could choose to waive the requirement for clinical trials, or reduce the required size or duration of the trial, if there is a scientific justification for doing so.

The BPCIA does not specify the particular dangers against which the switching requirement guards. Two possibilities seem likely: switching between innovator and follow-on biologics may increase the risk of an unwanted immune response, or may promote resistance to the therapeutic.

A patient has greater risk of a dangerous immunogenic response to a biologic than a small molecule drug for two reasons. First, biologics simply engender higher immune responses than small molecules.¹⁹⁹ This is probably because biologics, more than small-molecule drugs, resemble the foreign pathogens which the immune system has evolved to recognize. In addition, certain biologic therapies, like human growth hormones, are structurally related to proteins in the patient’s own body. Thus, an immune response against the therapeutic may also attack the patient’s own related protein; this is an autoimmune disease. While an immune response solely against a therapeutic is dangerous because it reduces the therapeutic’s efficacy, an autoimmune response that also attacks a patient’s own protein is even more worrisome.

If switching from an innovator biologic to a follow-on biologic raises an unwanted immune response, it might do so in one of two ways. In a first scenario, the follow-on biologic might simply be more immunogenic than the innovator biologic. In a second scenario, the innovator drug and follow-on biologic individually have the same immunogenicity, but a patient who switches back and forth between them raises a synergistic immune response.

The first scenario should be identified easily in human immunogenicity studies. One example is the approval of Avonex, a biologic for treating multiple sclerosis.²⁰⁰ Two companies, Biogen and Bioferon, manufactured Avonex using different methods, using different cell lines in their manufacturing process.²⁰¹ Biogen demonstrated that its manufacturing process resulted in lower immunogenicity.²⁰² Although in this example, the second manufacturer produced a biologic with a superior immunogenicity profile, it illustrates that two similar biologics can have different immunogenicity profiles.

In the second scenario, two equally immunogenic biologics produce a synergistic immune response.²⁰³ This concern is plausible, but the few studies that have been performed suggest that the frequency of a synergistic immune response to two biosimilars is low.²⁰⁴ A retrospective study identified a small number of patients that had switched between Genotropin and Omnitropin, two related but non-identical growth

¹⁹⁶42 USC §262(k)(4)(A)(ii).

¹⁹⁷*Id.*

¹⁹⁸Torti, *supra* at 9–10.

¹⁹⁹*Id.* at 1.

²⁰⁰Woodcock *et al.*, *op. cit.* n. 185, at 441.

²⁰¹*Id.*

²⁰²*Id.*

²⁰³Part 15 Public Hearing transcript, Draft Guidances Relating to the Development of Biosimilar Products (May 11, 2012), p. 220.

²⁰⁴*Id.* at 364–365.

hormones.²⁰⁵ No adverse events were reported.²⁰⁶ A study of patients switched from an innovator growth hormone, Humatrope, to Valtropin, a follow-on biologic approved in Europe, observed no significant change in immunogenicity or efficacy.^{207,208} In fact, the switched patients produced a slightly lower frequency (2.0%) of anti-growth hormone antibodies than did the patients receiving only Valtropin (3.1%), but the report cautions that this study of 45 patients is too small to allow firm conclusions about immunogenicity.²⁰⁹ These studies suggest that a patient that switches between related biosimilars is not at a higher risk of an unwanted immune response. On the other hand, the Deputy Commissioner of FDA in 2008 stated, “For many follow-on protein products, there is a known significant risk in repeatedly switching between products and a resulting negative impact on both patient safety and/or effectiveness.”²¹⁰ However, examples of the risk actually coming to pass are not provided.

The risk that switching biologics will cause a synergistic immune response, though plausible, has not materialized. Caution is appropriate in the early chapters of a pathway for approval of interchangeable biologics. However, if over time, studies indicate that the risk of switching is low, FDA should consider loosening the switching requirement for interchangeable biologics.

It is also worth considering whether the switching requirement helps guard against patients becoming resistant to a therapy. At this point, the concern is theoretical; I am not aware of reports of drug resistance caused by a patient switching between similar biologics. Not every drug is equally likely to lead to drug-resistance. The risk of drug-resistance is generally greatest in diseases where the therapeutic kills or otherwise inhibits an unwanted cell, and natural selection pressures the unwanted cell to develop resistance. If an innovator biologic and follow-on biosimilar act by different mechanisms, switching between them might foster drug resistance by allowing a slightly resistant cell population to recover and multiply. Under this approach, a sponsor of a therapeutic for resistance-prone diseases like cancer or an infectious disease would need to conduct more extensive trials than the sponsor of a therapeutic for, *e.g.*, diabetes or an inherited genetic disorder. Accordingly, FDA should release guidance indicating the product classes in which clinical studies are expected to be most necessary to show interchangeability. If clinical trials are generally required to show that switching is safe, the switching requirement may be the most stringent requirement to meet in demonstrating interchangeability. On the other hand, if a sponsor could show that a follow-on biologic acts by the same mechanism as the innovator biologic, this finding would suggest that switching would not lead to resistance.

Current law on generic small molecule drugs does not inform the switching requirement for interchange-

able biologics. The Hatch-Waxman Amendments do not prohibit pharmacists from substituting a generic drug for a brand-name one.²¹¹ In fact, most states explicitly allow pharmacists to do so, and some even mandate switching under certain circumstances.²¹² Thus, Congress considers there to be minimal risk when a patient switches to a generic small molecule drugs, but considers that biologics may present a substantial risk.

Congress may have deliberately made the switching requirement difficult to meet in order to classify most follow-on biologics as biosimilars and not interchangeable biologics. If frequent switching between biologics was Congress’s major concern, Congress could have addressed it by requiring labels warning against switching, or allowing a pharmacy to substitute an interchangeable drug at the beginning of a course of treatment, but not at the middle.²¹³ Denying “interchangeability” status to most biosimilars will make it harder for follow-on companies to win market share away from innovators, will shift the balance of purchasing power from pharmacies to health care providers, and will speed the entry of multiple biosimilars onto the market by avoiding the temporary exclusivity period an interchangeable biologic enjoys.

V. CONCLUSION

Enactment of the BPCIA was a crucial first step in creating a workable abbreviated pathway for licensing biosimilars. The BPCIA created the broad outlines of categories for biosimilar and interchangeable biologic therapeutics. In its draft guidance documents, FDA has begun to fill in the details. Clearly, additional guidance from FDA and the courts will be essential in creating a fair and consistent framework for licensing follow-on biologics.

²⁰⁵Torti, *supra* at 6.

²⁰⁶*Id.* at 5–6.

²⁰⁷European Medicines Agency. Valtropin: EPAR - Scientific Discussion, May 31, 2007; *available at* www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000602/WC500047158.pdf, 23.

²⁰⁸Dowlat, How safe are biosimilars? Implications of FDA and EMA Guidances and European experience since 2006. Regulatory Focus May 2012, p. 5.

²⁰⁹European Medicines Agency. Valtropin EPAR, *supra* at 23.

²¹⁰Torti, *supra*, at 4.

²¹¹21 USC §§355(j) and 355(b)(2).

²¹²ASPE Issue Brief, “Expanding the Use of Generic Drugs” (2010); *available at* <http://aspe.hhs.gov/sp/reports/2010/Generic-Drugs/ib.shtml>

²¹³Stroud, *supra* at 627.