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THE BIOSIMILARS ACT: THE UNITED STATES' ENTRY INTO REGULATING BIOSIMILARS AND ITS IMPLICATIONS

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ABSTRACT

The Patient Protection and Affordable Care Act is most well-known for creating a mandate requiring individuals to have health insurance. However, another provision of the Act, the Biologics Price Competition and Innovation Act, created a new process for companies to introduce biosimilars, products that are highly similar to licensed drugs in terms of purity, safety, and potency, but have minor differences in the inactive ingredients. This provision seeks to alleviate strain on companies introducing biosimilars by creating an abbreviated pathway for their approval by the Food and Drug Administration, similar to an Abbreviated New Drug Application under the Hatch-Waxman Act. This article provides a comprehensive overview of the Biologics Price Competition and Innovation Act and contrasts it with the Hatch-Waxman Act and European Law on Biosimilars. Strategies for patent claiming and resolving patent disputes are then discussed.

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INTRODUCTION

On March 23, 2010, the Patient Protection and Affordable Care Act ("Affordable Care Act")¹ was officially signed into law, which included provisions that greatly altered the delivery of healthcare services in the United States. The Affordable Care Act quickly became the center of a national debate as challenges regarding the constitutionality of certain provisions surfaced.² A key provision, which became known as the individual mandate, required citizens to either maintain "minimum essential" health insurance coverage or pay a fine.³ This provision was at the heart of efforts to render the Affordable Care Act unconstitutional and was ultimately reviewed by the Supreme Court of the United States.⁴ Many believed that if the individual mandate was deemed unconstitutional, the entire Affordable Care Act would fall, thus negating the provisions entirely unrelated to the individual mandate, including provisions that related to the regulation of biologics.⁵ Indeed, unbeknownst

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¹ Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

² See *Health Care Reform and the Supreme Court (Affordable Care Act)*, N.Y. TIMES, http://topics.nytimes.com/top/reference/timestopics/organizations/s/supreme_court/affordable_care_act/index.html (last updated Dec. 6, 2012).

³ 26 U.S.C. § 5000A(b)(1) (2012).

⁴ Nat'l. Fed'n of Indep. Bus. v. Sebelius, 132 S. Ct. 2566 (2012).

⁵ *Supreme Court Health-Care Decision: 3 Scenarios*, WASH. POST. (June 21, 2012), <http://www.washingtonpost.com/wp-srv/special/politics/health-care-decision/three-scenarios/index.html>.

to many individuals outside of the Biotechnology industry, the Affordable Care Act included the Biologics Price Competition and Innovation Act of 2009 (“Biosimilar Act” or “the Act”).⁶

On June 22, 2012, the Supreme Court held that the individual mandate and provision were constitutional, thereby preserving the Healthcare Act, including the Biosimilar Act.⁷ This Article discusses key provisions of the Biosimilar Act, including the newly-created abbreviated approval pathway for biologics. The pathway’s requirements, such as demonstrating biosimilarity or interchangeability, and the exclusivities granted under law will also be discussed. The proposed process and structure of the pathway will be compared and contrasted with the Hatch-Waxman Act, which addresses the abbreviated pathways for generic drugs, and the current abbreviated approval processes for biologics in Europe. Lastly, this article discusses implications for patenting biosimilar inventions and resolving patenting disputes.

I. REGULATION OF BIOLOGICS

A. General Principles

The last several decades produced great advances in the understanding of biological systems.⁸ This understanding led to the birth of the biotechnology industry, which provided a multitude of scientific advancements and innovations.⁹ Like any radical shift or advancement, however, regulations relating to these advancements required frequent, and sometimes highly-contested, government interventions.¹⁰ These interventions have come in the form of clarifying existing laws as well as forming new laws and regulations. Indeed, it was only about thirty years ago that the Supreme Court was tasked with determining whether human-made microorganisms were eligible for patent protection,¹¹ and the term “biotechnology” was not universally defined until about twenty years ago.¹² Since its infancy, the

⁶ See Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–03, 124 Stat. 119, 804–21 (2010) (codified as amended in scattered sections of 21 and 42 U.S.C.). The Biologics Price Competition and Innovation Act of 2009 is Title VII, Subtitle A of the Affordable Care Act. *Id.* § 7001, 124 Stat. at 804.

⁷ *Nat’l. Fed’n Of Indep. Bus.*, 132 S. Ct. at 2608. The Court determined that another provision of the Act was unconstitutional, however, and deemed it severable from the Act. *Id.* at 2607–08.

⁸ NAT’L INST. OF STANDARDS AND TECH., U.S. DEPT OF COMMERCE, MEASUREMENT CHALLENGES TO INNOVATION IN THE BIOSCIENCES: CRITICAL ROLES FOR NIST 1 (2009).

⁹ Whitney Tiedemann, *First-to-File: Promoting the Goals of the United States Patent System as Demonstrated Through the Biotechnology Industry*, 41 U.S.F. L. REV. 477, 483 (2007).

¹⁰ See, e.g., U.S. DEPT OF AGRIC., BIOTECHNOLOGY REGULATORY SERVICES: COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY 3 (2006) (explaining the federal government’s role in creating regulations in the beginning stages of biotechnology).

¹¹ *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

¹² See, e.g., U.N. Convention on Biological Diversity art. 2, June 5, 1992, 1760 U.N.T.S. 79; 31 I.L.M. 818. The United Nations and the World Health Organization each accepted the 1992 Convention on Biological Diversity (Convention). The Convention defined biotechnology as “any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products and processes for specific use.” *Id.*

biotechnology industry has developed an array of therapeutic and medicinal products.¹³ Given the less-predictable nature of biologics as compared to traditional medicines, however, the development, manufacture, and administration of biologic products to the public in a safe and effective manner have been associated with slow development phases and high treatment costs.¹⁴

The Biosimilar Act aims to balance the public policy of ensuring the availability of affordable medicinal and therapeutic biologics against the competing, but equally important, considerations of the intense investment and risk required to develop and manufacture effective and safe biologic products.¹⁵

B. Biological Substances Within the Act's Scope

Most biological products receive regulatory approval in the form of a biologics license application ("BLA") under section 351 of the Public Health Service Act.¹⁶ Prior to the Biosimilar Act, follow-on biosimilar products seeking regulatory approval under the Public Health Service Act were required to submit a regular approval application under section 351(a) in order to obtain licensure from the Food and Drug Administration ("FDA").¹⁷ Thus, regardless of any similarity, biosimilar applicants were required to undergo the same licensing guidelines as were required to market an entirely new and different biologic product in the United States (commonly referred to as "innovator products") for which they were modeled after.¹⁸

Under the Act, developers of a "biosimilar" product (or inclusive "interchangeable" product) retain the option to request abbreviated approval by the FDA.¹⁹ Not every substance comprising biological materials is subject to the provisions of the Biosimilar Act. As indicated above, not all biologic products are licensed under the Public Health Service Act, which defines "biologics" as:

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

¹³ See Jean-Louis Prugnaud, *Similarity of Biotechnology-Derived Medicinal Products: Specific Problems and New Regulatory Framework*, 65 BRIT. J. CLINICAL PHARMACOLOGY 619, 619 (2008).

¹⁴ FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL TECHNOLOGIES, at i (2004).

¹⁵ Joanna T. Brougher & David A. Fazzolare, *Will the Biosimilars Act Encourage Manufacturers to Bring Biosimilars to Market?*, FOOD & DRUG POL'Y F., Mar. 9, 2011, at 1, 5. In 2011, the average cost for a biologic therapeutic or medicinal product in the US was estimated at \$16,000 annually with some costing \$120,000. ANDREW F. BOURGOIN, WHAT YOU NEED TO KNOW ABOUT THE FOLLOW-ON BIOLOGIC MARKET IN THE U.S.: IMPLICATIONS, STRATEGIES, AND IMPACT 1 (2011), available at <http://thomsonreuters.com/content/science/pdf/ls/newport-biologics.pdf>.

¹⁶ 42 U.S.C. § 262(a) (2012); see also 21 C.F.R. 601.2 (2013).

¹⁷ James V. DeGiulio, *FDA Guidance Uncertainty May Deter Use of Abbreviated Biosimilar Approval Pathway*, 6 LIFE SCI. L. & INDUSTRY REP. 467, 467 (2012).

¹⁸ *Id.*

¹⁹ *Id.*

to the prevention, treatment, or cure of a disease or condition of human beings.²⁰

Some proteins, however, such as insulin and human growth hormones, are subject to approval under section 505 of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”).²¹ In this regard, the Biosimilar Act is unclear exactly as to the definite boundaries of what will be deemed a “protein,” “peptide,” or a “chemically-synthesized polypeptide.”²² The FDA, which is the governmental agency tasked with reviewing the biologics license applications, has provided guidance documents on the categorization of biological substances.²³ These documents provide guidance as to how the FDA intends to categorize many substances, including those provided below in Table 1. Using the FDA’s guidance, Table 1 also provides clarification of whether the product would be licensed as a biological product under the Public Health Service Act or as a drug under the FD&C Act.²⁴

Table 1. Definitions of Key Biologic Substances and Implicated Licensure

Polymer	Defined As
Protein <i>Biological product after 3/23/2020</i>	More than 40 amino acids Specific, defined sequence
Peptide <i>Drug unless also a biological product (e.g., vaccine, blood product)</i>	40 or fewer amino acids
Chemically synthesized polypeptide <i>Drug unless also a biological product (e.g., vaccine, blood product)</i>	Fewer than 100 amino acids Entirely synthetic

²⁰ 42 U.S.C. § 262(i)(1).

²¹ *Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm> (last visited Feb. 12, 2013); 21 U.S.C. § 355 (2012).

²² See 42 U.S.C. § 262(i)(1) (explaining that the definition of “biological product” includes “protein,” but excludes “chemically synthesized polypeptide,” and none of these terms are defined within the Act).

²³ *Guidance for Industry on Biosimilars: Q&As Regarding Implementation of the BPCI Act of 2009: Questions and Answers Part II*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm271790.htm> (last updated Feb. 9, 2012). The FDA has issued draft guidance documents relating to: (1) Scientific Considerations; (2) Quality Considerations; and (3) Q&A. *Id.*

²⁴ *Id.*

As shown in Table 1, substances categorized as proteins will be deemed “biological products” after March 23, 2020.²⁵ Until then, proteins (as currently defined by the FDA’s guidance documents) will not be required to be submitted under section 351 of the Public Health Service Act, but may instead be submitted as a drug under the FD&C Act, subject to certain criteria.²⁶ During the transition period, it generally depends if there was already another protein in the same product class that was approved as a drug (but could be used as a reference product) for the protein.

C. Abbreviated Approval Process for Follow-On Products

1. Introduction

The most significant change made by the Biosimilar Act is the creation of an abbreviated approval scheme for follow-on biologics shown to be biosimilar with an approved reference product.²⁷ In this regard, the Biosimilar Act is the corollary to the Hatch-Waxman Act, which established abbreviated pathways for the approval of generic drug products in the United States.²⁸ Familiarity with the Hatch-Waxman Act, however, provides little guidance with the Biosimilar Act. Many of the differences between the two Acts stem from the natural differences between biologics and traditional drugs. As one example, biologics often come from diverse living sources, and thus, there is an increased chance of transmitting diseases and agents, including bacteria and viruses.²⁹ This lends itself to a legal framework having more validation and controls. Biologics are also more sensitive to environmental conditions; therefore, more stringent production and distribution facilities are required.³⁰ Given the organic nature of biologics, however, most traditional sterilization techniques are not viable options.³¹

²⁵ *Id.*

²⁶ See 42 U.S.C. § 355 (2012) (identifying application requirements for the safety and effectiveness “of the drug **or** biological product”) (emphasis added); Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 563–64 (2008) (“Most biologics, however, are approved for marketing under provisions of the Public Health Service Act (PHSA). Because biologics typically meet the definition of ‘drugs’ under the FDCA, they are governed by that statute as well.”). This transition period is described in the Affordable Care Act. See Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(e), 124 Stat 119, 817 (2010).

²⁷ See Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804–08 (2010) (codified as amended at 42 U.S.C. § 262(k)). The Act sets forth a heightened standard of “interchangeable,” *id.*, which will be described in greater detail below.

²⁸ The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 21 U.S.C.). The Hatch-Waxman Act is formally known as the Drug Price Competition and Patent Term Restoration Act of 1984.

²⁹ See, e.g., *The Basics of Biologics*, ARTHRITIS TODAY, Jan.–Feb. 2013, at 56, 57 (discussing the risks of biologics).

³⁰ Am. Pharmacist Ass’n, *The Biosimilar Pathway: Where Will It Lead Us?*, PHARMACY TODAY, Dec. 2011, at 67, 68; Gitter, *supra* note 26, at 564 (citing commentators’ statements: “[R]egulation [of biologics] is focused on ‘rigid control of the manufacturing process,’ which reflects the particular scientific and historical characteristics of biopharmaceuticals”). A biologic license application must

The abbreviated approval scheme requires the filing of a biosimilars application under an entirely new sub-section—section 351(k)—of the Public Health Service Act that was created through the Affordable Care Act.³² Given the creation of the new subsection, these abbreviated applications are commonly referred to as “351(k) applications,” including throughout this article.

2. Key Definitions of a Biosimilars Application – “351(k) application”

The Affordable Care Act amended section 351 of the Public Health Services Act to include new subsection (k) which sets forth the requirements for licensing biological products as biosimilar to a reference product.³³ Fortunately, the Biosimilar Act specifically addresses what constitutes biosimilarity and defines qualifying reference products.³⁴

Each biologic product seeking expedited approval under 351(k) is compared, and ultimately judged against, a prior-approved biologic product that was licensed under the full approval process.³⁵ This “reference product” serves as a standard for safety, purity, and potency.³⁶ An important issue for many biosimilar applicants is the Biosimilar Act’s requirement that the prior-approved reference product be a “single product.”³⁷ Thus, the abbreviated process cannot be used for so-called combination biologics that consist of multiple biologics. Even if an applicant can successfully demonstrate that a combination biologic is merely a safe combination of two prior-approved biologic products, approval for any combination products will have to be sought through the regular approval process.

The Biosimilar Act further requires that the proposed biologic seeking expedited approval be “biosimilar” to the reference product. As set forth in the Act:

The term “biosimilar” or “biosimilarity”, in reference to a biological product that is the subject of an application under subsection (k), means—

demonstrate: (1) the standards regarding safety, purity, and potency are met; (2) the manufacturing, processing, packaging, and/or holding facility meets certain standards to ensure the product’s safety, purity, and potency are maintained; and (3) the applicant must allow FDA to inspect the aforementioned facility. Gitter, *supra* note 26, at 574.

³¹ See Daphne Allen, *Sterilization: Using Radiation on EtO for Biologics*, PMPNEWS.COM (May 29, 2008), <http://www.pmpnews.com/article/sterilization-using-radiation-or-eto-biologics> (discussing how biologics cannot generally survive the same sterilization processes which other drugs may).

³² DeGiulio, *supra* note 17, at 467.

³³ Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804–08 (2010) (codified as amended at 42 U.S.C. § 262(k) (2012)). Applicants must also demonstrate (1) the same mechanism of action as the reference product (if it is known), (2) demonstrate the condition(s) of use previously approved for the reference product, (3) utilize the same route of administration, dosage form, strength as reference product, and (4) ensure the proposed product must be manufactured, processed, packed, or held in a facility that meets standards for maintaining safety, purity, and potency. *Id.*

³⁴ 42 U.S.C. §§ 262(i)(2), (4).

³⁵ See *id.* § 262(i)(3).

³⁶ See *id.* § 262(i)(2)(B).

³⁷ *Id.* § 262(i)(4).

(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.³⁸

3. Demonstrating Biosimilarity

The Act further sets forth that biosimilarity is proved through (1) analytical studies that demonstrate the highly similar features, as compared to the reference product; (2) animal studies, including the assessment of toxicity, and (3) one or more clinical studies that are sufficient to demonstrate safety, purity, and potency.³⁹

The Act was written with the correct perspective that biological products are, by nature, more variable in their properties than traditional drugs, and as such, require a more flexible framework for establishing biosimilarity. An example of this is readily shown by the third requirement, which focuses on the clinical studies for approval. This section requires “a clinical study or studies [that include the] assessment of immunogenicity and pharmacokinetics or pharmacodynamics.”⁴⁰ The Act further specifies that a study or studies must be “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.”⁴¹

a. FDA Draft Guidance Documents

The FDA has issued three draft guidance documents to assist applicants with the process of preparing and submitting an application for a proposed biosimilar product:

- Scientific Considerations
- Quality Considerations
- Q&A⁴²

The FDA opened a comment phase for the draft guidance documents, which is now complete; however, to date, no final guidance documents have been issued by the

³⁸ *Id.* § 262(i)(2) (emphasis added).

³⁹ 42 U.S.C. § 262(k)(2)(A)(i)(I) (2012).

⁴⁰ 42 U.S.C. § 262(k)(2)(A)(I)(cc) (emphasis added).

⁴¹ *Id.*

⁴² *Fact Sheet: Issuance of Guidances on Biosimilar Product Development*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm291197.htm> (last updated Feb. 9, 2012).

FDA.⁴³ Importantly, the FDA guidance documents may indicate that a certain product class is *ineligible* for approval for a license due to science and experience with the particular product class, although the guidance documents may later be modified or reversed.⁴⁴

i. Step-Wise Approach

Unlike many government approval processes, including those for seeking drug approval, the FDA draft guidance document pertaining to scientific considerations advocates a “stepwise approach” for demonstrating biosimilarity between the reference product and the biosimilar applicant.⁴⁵ Thus, the FDA may, at its discretion, determine whether any of the comparisons are unnecessary and recommend presenting development plans and a milestone schedule.⁴⁶ The FDA will provide feedback on a case-by-case basis.⁴⁷

The FDA recommends beginning with structural and functional characterization of both products.⁴⁸ Depending on the outcome of these initial studies (and later-conducted studies), applicants would likely need to provide less data for easily characterized biological products. Similarly, the FDA’s scientific guidelines make concessions for the unknown and highly variable nature of biologics with the “stepwise approach,” which acknowledges that many product-specific factors can influence a product development program.⁴⁹ Thus, the assessment of one element may influence decisions about relevant data for the next step, and the extent of uncertainty of the biosimilarity may be evaluated to select the next steps to address that uncertainty.⁵⁰ Therefore, it is believed that applicants that meet with the FDA throughout the process (such as ensuring the data conveys an understanding of the mechanism(s) of action and the safety risks of the reference product) could expedite completion of the required comparative evidence.

⁴³ *Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259797.htm> (last updated Mar. 22, 2012); *FDA Issues Draft Guidance on Biosimilar Product Development*, FOOD & DRUG ADMIN., <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm291232.htm> (last updated Feb. 9, 2012).

⁴⁴ See FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 1 (2012) [hereinafter SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY].

⁴⁵ *Id.* at 7–8. According to the FDA, the products would be compared with regard to: structure, function, effectiveness, human pharmacokinetics (PK), human pharmacodynamics (PD), clinical safety, clinical immunogenicity, and animal toxicity. *Id.* at 2.

⁴⁶ *Id.* at 4.

⁴⁷ Deborah L. Lu, *Draft Biosimilars Approval Guidelines Released by FDA: More Questions than Answers?*, NAT’L L. REV. (Apr. 12, 2012), <http://www.natlawreview.com/article/draft-biosimilars-approval-guideline-released-fda-more-questions-answers>.

⁴⁸ SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 7. The functional characterization studies include (1) fingerprint, which is the quantification of various product attributes and (2) the extent of characterization related to the need for studies.

⁴⁹ *Id.*

⁵⁰ *Id.*

It is worth noting that the biological product needs to be shown to be “biosimilar” (or interchangeable) and not superior to the reference product for which it is being evaluated.⁵¹ Thus, clinical studies need to demonstrate that a proposed biologic product has neither decreased nor increased activity compared to the reference product.⁵² For example, increased activity of a biologic product may mean more adverse side effects, which would preclude being considered biosimilar. Further, if the increased activity results in a superior product (e.g., improved efficacy), it may result in the FDA treating the biologic as a new product with superior efficacy (e.g., under section 351(a) of the Public Health Service Act).⁵³ Conversely, if the studies demonstrate decreased activity, as compared to the reference product, this would also preclude a proposed biologic product from being “biosimilar” and thus a successful licensure of the proposed product.⁵⁴ Therefore, only proposed products with the same activity are subject to licensing as biosimilar products.⁵⁵

ii. Totality of the Evidence

The FDA further advocates a “totality-of-the-evidence approach” in licensing biologics.⁵⁶ Similar to the “stepwise approach,” the totality approach appreciates the great variations in proteins, and thus the requisite approval process.⁵⁷ This risk-based approach foregoes rigid requirements for specific types of comparative data,⁵⁸ but instead looks for any clinically meaningful differences with respect to each of the following: safety, purity, and potency.⁵⁹ Thus, the “totality-of-the-evidence” determination will likely be informed by FDA input during the stepwise approach.⁶⁰

The FDA documents further address the impact of specific protein product complexity.⁶¹ In this regard, it is understood that the biologic product being applied for is likely not structurally identical to the reference product. Indeed, protein modifications and higher order structure may be affected by environmental conditions, including those inherent in the manufacturing process itself.⁶² As it is known in the biological sciences, structure dictates (or at least greatly affects) function, and thus, minor structural differences may have significant effects on safety, purity, and potency.⁶³ Therefore, an applicant may have to provide more

⁵¹ *Id.* at 17.

⁵² *Id.*

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.* at 8.

⁵⁶ *Id.* at 8.

⁵⁷ *Id.* at 2.

⁵⁸ See FOOD & DRUG ADMIN., U.S. DEPT OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 3 (1998) (referring to substantial evidence as “adequate and well-controlled investigations, including clinical investigations, by experts”).

⁵⁹ SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 8.

⁶⁰ *Id.* at 21.

⁶¹ *Id.* at 4–5.

⁶² *Id.* at 5.

⁶³ *Id.* at 4.

extensive data from analytical, animal, and clinical studies when analytical methodology is incapable of detecting relevant differences between two proteins.⁶⁴

1. Implications

From a legal perspective, the step-wise/totally-of-the-evidence approach poses some serious strategy considerations and raises possible concerns regarding the examination of these applications. The step-wise approach is based upon the total evidence.⁶⁵ In this regard, each 351(k) application for a biosimilar product must stand on its own.⁶⁶ Specifically, FDA approval of a 351(k) application must be based upon data in the 351(k) application and any publicly available information that may be available regarding the reference product from which the applied-for biosimilar is modeled.⁶⁷ The distinction of publically available information is an important one. Trade secrets submitted by innovators as part of a BLA license, under the full non-abbreviated process for the “reference product” for the biosimilar, are protected from public disclosure.⁶⁸ Thus, the biosimilar applicant cannot rely on these trade secrets.

The guidelines for trade secret protection, however, are still being finalized.⁶⁹ In this regard, it is common for government agents or employees, most familiar with specific technology, to be assigned to analyze technical applications from competitors.⁷⁰ For example, patent examiners at the United States Patent and Trademark Office (“USPTO”) are assigned to Art Groups.⁷¹ Art Groups are formed according to technological boundaries.⁷² As such, patent examiners in a single Art Group, or even closely related Art Groups, routinely examine patent applications from competitors regarding highly similar subject matter.⁷³

Therefore, questions regarding the FDA’s examination process and assignment of reviewers to the BLAs are natural and logical. For example, will 351(k) reviewers also review the “reference product’s” trade secrets? From an efficiency perspective, such reviewers may be best suited to fully understand the technology and the various issues, which will ensure that safety, potency, and purity are addressed.⁷⁴ Would

⁶⁴ *Id.* at 8–10.

⁶⁵ *Id.* at 21.

⁶⁶ *Id.* at 3–4.

⁶⁷ *Id.* at 4.

⁶⁸ Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L.J. 285, 289 (2011).

⁶⁹ See Krista H. Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 756 (2012).

⁷⁰ See, e.g., IAIN M. COCKBURN ET AL., ARE ALL PATENT EXAMINERS EQUAL? EXAMINERS, PATENT CHARACTERISTICS, AND LITIGATION OUTCOMES 5 (2002) (explaining how patent applications are assigned to examiners).

⁷¹ *Id.*

⁷² See *id.*

⁷³ See ANNEMARIE L. M. FIELD ET AL., PATENT EXAMINER RECRUITMENT: AN INTERACTIVE QUALIFYING PROJECT FOR THE USPTO 81 (2007), available at <http://www.wpi.edu/Pubs/E-project/Available/E-project-121207-102952/unrestricted/USPTOFINALREPORT.pdf>.

⁷⁴ *Cf. Id.* (explaining how patent examiners become “experts in [their] field” by working with one type of technology).

this, however, result in improper reliance? For example, would such review processes result in inadvertent reliance on an innovator's trade secrets regarding the reference product? Even if the FDA reviewer did not explicitly disclose the trade secrets, could they be inferred in the reviewer's acceptance of limited data or otherwise forego the need for different or additional tests?

In April 2012, Abbott Laboratories ("Abbott") submitted a Citizen Petition⁷⁵ requesting that the Commissioner of the FDA confirm that it will not take any action with respect to a biosimilar application that cites, as its reference product, "Abbott's BLA 125057 for Humira (adalimumab) or any other product for which the biologics license application (BLA) was submitted to the FDA prior to March 23, 2010, the date on which the [Act] was signed into law."⁷⁶ According to Abbott, it:

had no notice, or reasonable expectation, that the agency would use its trade secrets to approve another company's product[, and in fact, had] developed and submitted those trade secrets in reasonable reliance on FDA's lack of legal authority to approve biosimilars, confirmed by years of agency statements that it lacked such authority.⁷⁷

In May 2012, the FDA solicited comments via a public daylong meeting in which others voiced concerns over the need for safeguards to protect inadvertent trade secret disclosure.⁷⁸

An increased risk of trade secret exposure may warrant greater reliance of patent protection for innovations that may be novel and non-obvious.⁷⁹ This, however, may not be a viable option for those innovations where it is hard to demonstrate infringement—such as manufacturing processes conducted within a competitor's factory.⁸⁰ This is also not a feasible option for those applications for which foreign protection is sought, given the fact that a foreign filing license requires a Request for Non-Publication to be rescinded within a relatively early timeframe.⁸¹

⁷⁵ Letter from Covington & Burling LLP, on behalf of Abbott Laboratories, to Commissioner of Food and Drugs (Apr. 2, 2012), *available at* <http://patentdocs.typepad.com/files/abbotts-citizen-petition.pdf>. The Petition was submitted under 21 C.F.R. 10.30 and section 351 of the Public Health Service Act (as amended by the Act). *Id.*

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ *Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing; Request for Comments*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/NewsEvents/ucm265628.htm> (last updated July 6, 2012).

⁷⁹ See Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L.J. 285, 285–96 (2011), for a great discussion on how the Biosimilars Act implicates trade secrets.

⁸⁰ The patent laws account for some of the inherent difficulties in demonstrating infringement in such situations. For example, although plaintiffs ordinarily bear the burden of proving infringement, "there is a rebuttable presumption [under § 271(g)] that [an] imported product was made from [a] patented process if the court finds: '(1) that a substantial likelihood exists that the product was made by the patented process, and (2) that the plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable to so determine.'" *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314 (2011).

⁸¹ 37 C.F.R. § 1.213 (2013).

These are some of the issues that will need to be resolved before many biologic product manufacturers will rely on the abbreviated pathway.

2. *State of the Art*

The best indication of what to expect comes from the FDA's draft guidance document regarding Quality Considerations, which indicates the need for relevant, analytical studies.⁸² In this regard, not all biologics may be suitable for licensure as a biosimilar biological product.⁸³ For example, if the state-of-the-art technology cannot adequately characterize the reference and proposed products, a biosimilarity application may not be appropriate.⁸⁴ Another consideration may be that, during manufacturing, an applicant might aim to target physiochemical and functional properties of the reference product to increase the possibility of demonstrating that the products are highly similar.⁸⁵

Acceptance criteria are based on the totality of the analytical data, and the FDA's guidance documents encourage a side-by-side, comparative analysis of the proposed and reference products across various lots and timeframes.⁸⁶ For example, the FDA's guidance document related to Quality Considerations recommends performing a number of analytical studies to establish quality attributes in order to define the proposed product for comparison to the reference product.⁸⁷ Analytical characterization is further essential in designing the product manufacturing process and development studies to be able to effectively demonstrate biosimilarity of a proposed product to a reference product.⁸⁸

The FDA guidance document related to Scientific Considerations addresses general scientific principles in conducting studies to demonstrate the biosimilarity of a proposed product.⁸⁹ In particular, manufacturing process considerations are discussed because differences in biological systems may affect structure, and thus, function of a product.⁹⁰ Variations in any of the cell line, raw materials, equipment, processes, controls, and acceptance criteria can each contribute to producing a

⁸² FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PROTEIN PRODUCT 4 (2012) [hereinafter QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY].

⁸³ *Id.*

⁸⁴ SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 10.

⁸⁵ QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 82, at 6. Analytical procedures would potentially be capable of characterizing each of the following: desired product, product-related substances, and impurities. *Id.* With respect to structure, the FDA's draft guidance document regarding Scientific Considerations indicates that the expression construct for the proposed product will encode the same primary amino acid sequence as the reference product, while minor structural modifications (e.g., N- or C- terminal truncations) should be justified by the Applicant as not affecting safety or effectiveness. SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 9.

⁸⁶ QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 82, at 7.

⁸⁷ *Id.* at 6. Quality attributes may include identity, quantity, purity, potency, consistency, three-dimensional structure, and identification of impurities and product-related substances. *Id.*

⁸⁸ *Id.* at 15.

⁸⁹ SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 7.

⁹⁰ *Id.* at 5.

biological product that is different from a reference product.⁹¹ An applicant seeking to establish biosimilarity, where the reference product is made by a different manufacturer, will, therefore, likely need to present more data than a different process from the same manufacturer to establish biosimilarity of the proposed product to a reference product. The guidance document recommends a robust analytical comparison of a proposed product and a reference product, with respect to a number of structural aspects.⁹² Moreover, testing for multiple lot-to-lot variability of proposed and reference products and of finished dosage forms is also encouraged.⁹³ Consequently, applications for biosimilar licenses may not be appropriate for biological products that cannot be well characterized analytically.⁹⁴

Data from a non-U.S. licensed reference product, to compare to a proposed biosimilar product, may be acceptable, including animal or clinical studies, to meet part of the scientific requirements.⁹⁵ To use data from a non-U.S. licensed reference product, however, the applicant must be able to establish a scientifically relevant bridge between the non-U.S. licensed reference product and the U.S. licensed reference product.⁹⁶

iii. Safety, Purity, Potency

As indicated above and elsewhere in the Affordable Care Act, the determination of biosimilarity is based upon the three main factors of safety, purity, and potency.⁹⁷ Safety refers to the relative freedom from harmful effects, either direct or indirect, when a product is prudently administered to a recipient.⁹⁸ Safety also takes into consideration the character of the product in relation to the condition of the recipient.⁹⁹ Purity refers to the relative freedom from extraneous matter in the finished product, regardless of whether or not it is harmful to the recipient or deleterious to the product, including (but not limited to) relative freedom from residual moisture or other volatile substances and pyrogenic substances.¹⁰⁰ Potency refers to the specific ability or capacity of a product to yield a given result, which is indicated by appropriate laboratory tests.¹⁰¹

The FDA recognizes that certain instances of licensed biosimilar products may require a post-marketing study to evaluate safety risks.¹⁰² Further, rare safety risks

⁹¹ *Id.* at 5–6.

⁹² *Id.* at 9. Structural aspects may include primary structures (e.g., amino acid sequence), higher order structures (e.g., 2°, 3° and 4° structure, aggregation), enzymatic post-translational modification (e.g., glycosylation and phosphorylation), potential variants (e.g., protein deamidation and oxidation), intentional chemical modification (e.g., PEGylation sites and characteristics). *Id.*

⁹³ *Id.*

⁹⁴ *Id.* at 10.

⁹⁵ *Id.* at 6.

⁹⁶ *Id.*

⁹⁷ *Id.* at 8.

⁹⁸ 21 C.F.R. § 600.3(p) (2013).

⁹⁹ *Id.*

¹⁰⁰ *Id.* § 600.3(r).

¹⁰¹ *Id.* § 600.3(s).

¹⁰² SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 20.

may be identified in post-marketing monitoring, due to studying a larger population size than in prior clinical trials.¹⁰³ Some studies may consider safety and effectiveness concerns for the use of a reference product and set mechanisms in place for differentiating between adverse events associated with the proposed product versus the reference product.

iv. Interchangeability

It is readily conceivable that two different biosimilar candidates could each be “highly similar” to the same reference product, but less similar with respect to each other. It is equally conceivable that these same two candidates have “no clinically meaningful differences . . . [from] the reference product in terms of the safety, purity, and potency”¹⁰⁴ Thus, each of these two candidates may be considered biosimilar with respect to the reference product. Nonetheless, one of them may exhibit a higher degree of similarity with the reference product than the other and as such, may be a better product. In this regard, the Act recognizes that there are varying levels of biosimilarity. It further recognizes that there are public policy reasons to incentivize increased biosimilarity.¹⁰⁵ Thus, the Act encourages the production of biosimilar products that are “interchangeable.” A biological product is considered “interchangeable”¹⁰⁶ if:

(A) The biological product—

(i) is *biosimilar* to the reference product; and

(ii) can be expected to produce the same *clinical result as the reference product in any given patient*; and

(B) for a biological 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*.¹⁰⁷

The Act further clarifies that a product shown to meet these standards “means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”¹⁰⁸

¹⁰³ *Id.*

¹⁰⁴ 42 U.S.C. § 262(i)(2)(B) (2012).

¹⁰⁵ See, e.g., Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7001(b), 124 Stat. 119, 804 (2010) (“It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established.”).

¹⁰⁶ The FDA has not yet established guidance for demonstrating interchangeability of a proposed product with a reference product.

¹⁰⁷ 42 U.S.C. § 262(k)(4) (2012) (emphasis added).

¹⁰⁸ *Id.* § 262(i)(3).

Thus, a biosimilar deemed interchangeable may be substituted by a pharmacy without requiring doctor approval.¹⁰⁹ Further, in the United States, obtaining licensure as the first interchangeable biosimilar is conferred with certain exclusivity rights, which are discussed immediately below.¹¹⁰

D. Exclusivities

1. Innovator Products

Innovator products, which are the first of their kind (and, as such, may later serve as a reference product for a biosimilar product), undergo the full licensing requirements set forth under section 351(a) of the Public Health Service Act.¹¹¹ Recognizing that such developments require large amounts of risk and capital investment, the Act grants such innovator products a twelve year period of exclusivity.¹¹² This exclusory period consists of four years of data exclusivity followed by eight years of market exclusivity.¹¹³ During the four years of data exclusivity, biosimilar applicants cannot rely on any data submitted by the innovator for consideration in the licensing of the innovator product.¹¹⁴ In fact, during this time, no biosimilar applications are even accepted by the FDA.¹¹⁵ Further, the remaining eight years of exclusivity (in the form of market exclusivity) ensures that the FDA cannot approve any biosimilar (or interchangeable) products until twelve years following the granting of a biologics license to the initial innovator product.¹¹⁶

An additional six months of exclusivity is given for those innovator products that are approved for pediatric use.¹¹⁷ If an orphan drug is produced, the exclusivity of the orphan drug remains either the later of the initial twelve years of the exclusivity period or seven years after the orphan.¹¹⁸ It is important to note that each of these exclusivities are with respect to any follow-on biologics that attempt to seek approval under the abbreviated approval pathway as being “biosimilar” or “interchangeable;” however, the exclusivities do not apply to any products approved under the full licensing process under section 351(a).¹¹⁹ Second, the exclusivities do not permit “evergreening” for a new indication, route, dosing schedule, form, delivery system,

¹⁰⁹ *Id.*

¹¹⁰ *Id.* § 262(k)(6).

¹¹¹ *Id.*; see also DeGiulio, *supra* note 17, at 467 (discussing the two pathways biosimilar applicants can choose).

¹¹² 42 U.S.C. § 262(k)(7)(A).

¹¹³ Compare *id.* § 262(k)(7)(A) (granting twelve years of exclusivity “after the date on which the reference product was first licensed”), with *id.* § 262(k)(7)(B) (requiring an applicant to wait “4 years after the date on which the reference product was first licensed” before an application can be filed).

¹¹⁴ 42 U.S.C. § 262(k)(7)(B) (2012).

¹¹⁵ *Id.*

¹¹⁶ *Id.* § 262(k)(7)(A).

¹¹⁷ *Id.* § 262(m)(2)(A).

¹¹⁸ Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(h), 124 Stat. 119, 821 (2010).

¹¹⁹ *Id.*

device, strength, or change in structure not resulting in a change in safety, purity, or potency.¹²⁰

2. Biosimilar/Interchangeable Products

Approval of the first, or any subsequent, biosimilar product based upon a reference product does not confer any right with respect to exclusivities. The first approved interchangeable biosimilar product, however, is granted between twelve and forty-two months of market exclusivity.¹²¹

E. European Regulations Regarding Biosimilar Licensing

1. Innovator Products

As indicated above, the FDA is tasked with approving biosimilars in the U.S.¹²² The process is yet to be fully defined and tested as the three draft guidance documents were issued less than a year ago. In the European Union (“EU”), the process has had a bit more time to develop.¹²³ In this regard, the European Medicines Agency (“EMA”), the agency tasked with reviewing biosimilar applications,¹²⁴ already has numerous guidelines, both drafted and adopted.¹²⁵ The general guidelines were published in 2005, and the first biosimilar was approved in the EU in 2006.¹²⁶ The EMA routinely issues “Concept Papers” that, among other things, provide recommendations on amending draft guidelines as well as revising guidelines.¹²⁷ Comments often are solicited based upon the Comment Papers.¹²⁸

The EMA’s guidelines are similar to the proposed “stepwise approach” set forth by the FDA’s guidance documents. Specifically:

¹²⁰ See Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV., 511, 514–15 (2011).

¹²¹ 42 U.S.C. § 262(k)(6) (2012).

¹²² *Id.* § 262(k)(5)(B).

¹²³ Grabowski et al., *supra* note 120, at 520.

¹²⁴ *Id.* These biosimilar applications are referred to as Biosimilar Marketing Authorization Applications.

¹²⁵ *Id.*

¹²⁶ Eur. Meds. Agency [EMA], Guideline on Similar Biological Medicinal Products, EMEA Doc. No. CHMP/437/04 (Oct. 30, 2005), available at http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf.

¹²⁷ The EMA’s collection of concept papers may be searched online at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/document_library_search.jsp&mid= (enter “concept paper” in the “Search by keyword in title” field; then click “Submit”).

¹²⁸ See e.g., *Comments from the Biotechnology Industry Organization on the ‘Concept Paper on the Revision of the Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues’*, EMA/CHMP/BMWP/572828/2011 (Dec. 31, 2011), available at <http://www.bio.org/sites/default/files/BIO%20Comments%20to%20EMA%20Concept%20Paper%2031%20Dec%202011.pdf>.

If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided. . . . ***The type and amount of additional data . . . shall be determined on a case by case basis*** in accordance with relevant scientific guidelines.¹²⁹

Approval by the EMA follows a Product Class-Specific guidance that looks to the EU guidelines and Concept Papers.¹³⁰ To date, there are guidance documents on the following product classes:

Interferon β , recombinant interferon α , recombinant follicle stimulation hormone, monoclonal antibodies, recombinant erythropoietins, low-molecular-weight heparins, recombinant human insulin, and somatropin¹³¹

Generally, non-clinical *in vitro* studies are first conducted, which determine whether a need exists for *in vivo* studies.¹³² Clinical studies will generally be initiated with pharmacokinetics¹³³ and pharmacodynamics,¹³⁴ followed by studies of clinical efficacy, clinical safety, extrapolation of indications, and pharmacovigilance.¹³⁵ To date, the EMA has approved fourteen biosimilars. Table 2 provides the biosimilars approved as compared with their respective reference products.

¹²⁹ Directive 2001/83, of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medical Products for Human Use, Annex, 2001 O.J. (L 311) 1, 100 (EC) (emphasis added).

¹³⁰ Grabowski et al., *supra* note 120, at 520–21.

¹³¹ *Multidisciplinary: Biosimilar*, EUR. MEDS. AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c (last visited Feb. 17, 2013) (listing all guidance documents).

¹³² EMA, Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (Draft) at 5, Nov. 18, 2010, EMEA Doc. No. CHMP/BMWP/403543/2010 (2010), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf.

¹³³ *Id.* at 6–9 (showing that clinical studies include studying design, sampling times, examining parameters of interest, and examining timing).

¹³⁴ *Id.* at 9 (explaining that markers are used as support, to establish comparability, and can be used as pivotal proof of comparability).

¹³⁵ *Id.* at 9–12.

Table 2. Biosimilar Products Approved by the EMA¹³⁶

Somatropin (Recombinant Human Growth Hormone)	
	<ul style="list-style-type: none"> • Omnitrope powder (somatropin) from Sandoz based on Pfizer's Genotropin®
	<ul style="list-style-type: none"> • Valtropin (somatropin) from Biopartners, based on Lilly's Humatrope®
Epoetin alfa and epoetin zeta products based on Janssen-Cilag's Eprex/Erypo (EPOs)	
	<ul style="list-style-type: none"> • Binocrit (epoetin alfa) from Sandoz
	<ul style="list-style-type: none"> • Epoetin Alfa Hexal (epoetin alfa) from Sandoz (Hexal)
	<ul style="list-style-type: none"> • Abseamed (epoetin alfa) from Medice
	<ul style="list-style-type: none"> • Silapo (epoetin zeta) from Stada
	<ul style="list-style-type: none"> • Retacrit (epoetin zeta) from Hospira
Filgrastim products based on Amgen's Neupogen® (Granulocyte Colony Stimulating Factor)	
	<ul style="list-style-type: none"> • TevaGrastim (filgrastim) from Teva
	<ul style="list-style-type: none"> • Ratiograstim (filgrastim) from Ratiopharm
	<ul style="list-style-type: none"> • Filgrastim ratiopharm (filgrastim) Ratiopharm (now withdrawn)
	<ul style="list-style-type: none"> • Biograstim (filgrastim) from CT Arzneimittel
	<ul style="list-style-type: none"> • Zarzio (filgrastim) from Sandoz
	<ul style="list-style-type: none"> • Filgrastim Hexal (filgrastim) from Hexal
	<ul style="list-style-type: none"> • Nivestim (filgrastim) from Hospira UK

2. Exclusivities

In the EU, innovator drugs obtain ten years of exclusivity consisting of an initial data exclusivity period of eight years, followed by two additional years of market exclusivity.¹³⁷ Similar to the U.S. approach, pediatric uses may result in an additional one-year extension to the market exclusivity (thus providing three years total market exclusivity).¹³⁸ Orphan innovator products are provided ten years

¹³⁶ *European Public Assessment Reports*, EUR. MEDS. AGENCY, <http://www.ema.europa.eu/ema/> (click "Find medicine" tab; then follow "Human medicines" hyperlink; select "Browse by type"; then select "Biosimilars" radio button; then click "Submit") (last visited Feb. 17, 2013).

¹³⁷ Brook K. Baker, *Ending Drug Registration Apartheid: Taming Data Exclusivity and Patent/Registration Linkage*, 34 AM. J.L. & MED. 303, 307–08 (2008).

¹³⁸ See Commission Regulation 1901/2006, of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Paediatric Use and Amending Regulation (EEC) No

market exclusivity, except pediatric orphan innovator products, which are granted twelve years market exclusivity.¹³⁹ Market exclusivity may be extended an additional year if the reference product sponsor obtains approval for a second new indication during the data exclusivity period.¹⁴⁰ Similar to the U.S., the EU does not grant exclusivities for biosimilar products.¹⁴¹ Unlike the U.S., however, the EU does not have a corresponding category for “interchangeable,”¹⁴² and as such, there is no automatic substitution for biologics in the EU.¹⁴³ Table 3 provides a summary of the exclusivities discussed thus far.

Table 3. Exclusivities in the European Union and United States

Exclusivity Indication	European Union	United States
Innovator Data Exclusivity	8 years	4 years
Innovator Market Exclusivity	2 years	8 years
Pediatric Extension	1 year market exclusivity	6 months
Orphan	10 years market exclusivity	Later of 12 years or 7 years after approval
Pediatric Orphan	12 years market exclusivity	Later of 12.5 years or 7.5 years after approval
Innovator Second Indication	If 2 nd indication approved during data exclusivity, then market exclusivity is extended 1 year	N/A
Biosimilar Exclusivity	None	None
Interchangeable Exclusivity	None	12–42 months

1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, art. 36(5), 2006 O.J. (L 378) 1, 13 (EC).

¹³⁹ *Id.* art. 37, 2006 O.J. (L 378) 1, 13 (EC).

¹⁴⁰ Jonathan Loeb, *Comparison of U.S. and European Biosimilar Regulation and Litigation*, BIOLEGALICS (Mar. 29, 2011), <http://www.biologics.com/fda-approval/comparison-of-us-and-european-biosimilar-regulation-and-litigation/>.

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ *Id.*

II. PATENTING CONSIDERATIONS

A. Introduction / General Principles

Innovators who first discover and seek approval of the innovator biologic product through the full regulatory approval process clearly would benefit from seeking coverage broad enough to cover its own product. With the advent of the biosimilar pathway for mimicking products, innovators must also be sure to consider the biosimilar landscape. As such, possible design-around options, including methods that may be less desirable, may be worthy of fully disclosing and claiming. From the biosimilar applicant's perspective, the biosimilar product should be designed to avoid overlapping the innovator's claim scope; however, alterations to the proposed biosimilar product cannot result in a molecule that is so changed that it is no longer biosimilar. Further, biosimilar applicants have an incentive to seek the "interchangeable" status for their products to obtain the twelve to forty-two months of exclusivity.¹⁴⁴

B. Combining Exclusivities

There is no requirement for entities to possess exclusionary patent rights in order to obtain any of the exclusivities set forth by the Biosimilars Act. Nor are there any maximum limits on overlapping patent rights and exclusivity periods.¹⁴⁵ Therefore, when feasible, it is highly recommended to pursue both patent rights and exclusivity periods under the Act to preserve multiple options against competitors. In this regard, each application will be examined by different government agencies (different fact-finders) and impose different burdens,¹⁴⁶ and in the end, will provide two different potential causes of action against competitors.¹⁴⁷

Patent rights remain important given the limitation of the exclusivity periods offered by the Biosimilar Act. First, exclusivity may not apply to all "follow on" products. For example, the twelve-year exclusivity period granted to innovator products only applies to (and thus blocks) products approved through the abbreviated biosimilar pathway.¹⁴⁸ Thus, a product that is truly "biosimilar" to the innovator product can be pursued through the regular application pathway, thereby avoiding the innovator product's exclusivity restrictions.

¹⁴⁴ 42 U.S.C. § 262(k)(6)(A)–(C) (2012).

¹⁴⁵ See Grabowski et al., *supra* note 120, at 557 (claiming exclusivity provides an "insurance policy" to the patent system); 35 U.S.C. § 154(a)(2) (granting patent rights for a term of twenty years from the filing date of the patent application).

¹⁴⁶ Compare 35 U.S.C. § 1(a) (establishing USPTO's authority to grant and issue patent), with 42 U.S.C. § 262(k)(5) (establishing FDA's authority to review 351(k) applications).

¹⁴⁷ Compare 35 U.S.C. § 271 (patent infringement), with 42 U.S.C. § 262 (FDA exclusivity period).

¹⁴⁸ 42 U.S.C. § 262(k)(7).

*C. Patent Claiming Strategies**1. Revised Patent Landscape*

On September 8, 2011, the United States Senate approved the Leahy-Smith America Invents Act ("AIA"),¹⁴⁹ finalizing congressional acceptance of the largest alterations in U.S. patent laws in over half of a century.¹⁵⁰ By far the most sweeping change included in the AIA is the transition from a "first to invent" system to a modified "first inventor to file" system.¹⁵¹ This change, combined with the provisions of the Biosimilars Act, creates a tension in striking the balance between conducting the necessary tests to support a full disclosure that will cover the innovative product and any biosimilar products against the requirement of being the first to file the requisite application.¹⁵²

Clearly, filing before a competitor is a key factor. This early filing, however, may not contain enough information (or adequately convey the information) to effectively block biosimilar products and/or protect later-determined commercial embodiments. This consideration is not limited to innovator products. For example, a biosimilar product made by novel and non-obvious processes may require efficient filing strategies to prevent other biosimilar competitors from entering the market and/or blocking the manufacture of the innovative product with novel processes and/or materials.¹⁵³ On the other end of the spectrum, a later filing date (even if more robust) may cause equally unfavorable outcomes. For innovators, failing to secure patent rights opens more opportunities for biosimilar products to enter the market before the costs of research and development can be recouped.¹⁵⁴ Similarly, any biologics manufacturer, regardless of being an innovator or a biosimilar manufacturer, can be blocked from selling their product. For example, an innovator who obtains the twelve-year exclusivity period under the Biosimilar Act may still be prevented from making or selling their product that has innovator exclusivity because it is blocked by a competitor's patent that was earlier filed.¹⁵⁵

¹⁴⁹ H.R. 1249, 112th Cong. (2011) (enacted).

¹⁵⁰ Candice Decaire et al., *Negotiating a New Legal Landscape: The Advent of Follow-On Biologics*, 46 U.S.F. L. REV. 1029, 1030 (2012).

¹⁵¹ *Id.*

¹⁵² *Id.* at 1059 (discussing the tension that a "first inventor to file" system causes between having an adequate written description and time required to perfect biologic molecules).

¹⁵³ *Id.*

¹⁵⁴ *Compare*, 35 U.S.C. § 154(a)(2) (2012) (establishing a patent term of twenty years from the date of application), *with* 42 U.S.C. § 262(k)(7) (protecting a reference product for only twelve years).

¹⁵⁵ *See* 35 U.S.C. § 271(a) (defining infringement as selling or offer to sell any patented invention); 35 U.S.C. § 283 (allowing injunctive relief as a remedy for infringement).

2. Claiming Strategies

As explained above, passage of the Biosimilar Act increases the importance of adequately describing alternative embodiments.¹⁵⁶ This remains true even for embodiments that may not be directly important to the specific biologic substance. For example, embodiments of less-commercial importance may still warrant strong protection. As one example, a specific biologics product may be produced with two different excipients; however, a second excipient causes manufacturing costs to rise or otherwise may be less desirable. Despite this second excipient being less preferred, it still may be an acceptable candidate for use with a biosimilar product.¹⁵⁷ Further, although it is currently less preferred at the time of filing the patent application, it may become more preferable as time passes. This may be due to results obtained during the regulatory approval process (either the full approval process or the abbreviated process). For example, safety results may suggest that an excipient, previously considered the top candidate, is less than ideal. In this regard, the FDA may require safety tests to be conducted following granting of the biologics license.¹⁵⁸ Other factors, such as external economic forces, may remove or minimize any disincentives for the second excipient or other ingredient.

Claiming strategies should consider claiming an entire genus as well as one or more species within the genus. For example, instead of claiming a preferred cell line (e.g., mammalian, cell line A), consider claiming the genus of “mammalian cell lines.” This strategy can also be implemented to claim overlapping or alternative ranges.¹⁵⁹ This may be advantageous, for example, when reciting cell growth and selection parameters or purification properties. Another strategy may consider utilizing “product by process” claims, if appropriate.¹⁶⁰ For example, patent applications are often drafted during the early stages of development.¹⁶¹ This will continue to be true in view of the modified first-to-file system imposed under the AIA.¹⁶² During these early stages of development, the biologic substance of interest may not be adequately characterized. In certain instances, the very nature of the biologic substance may

¹⁵⁶ See also Kate S. Gaudry, *Exclusivity Strategies and Opportunities in View of the Biologics Price Competition and Innovation Act*, 66 FOOD & DRUG L.J. 587, 614 (2011) (explaining that “there are more potential design-arounds for biologics” than for small-molecule drugs, thus demanding more alternative embodiments).

¹⁵⁷ See 42 U.S.C. § 262(i)(2) (2012) (allowing “minor differences in clinically inactive components” so long as there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency”).

¹⁵⁸ SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY, *supra* note 44, at 20.

¹⁵⁹ See Gaudry, *supra* note 156, at 619–20.

¹⁶⁰ See *Smithkline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1315 (Fed. Cir. 2006) (defining a product-by-process claim as one that defines a product based on the method or process by which it is made); FED. TRADE COMM’N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 31 (2009), *available at* <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf> (listing several types of claims appropriate for biologics).

¹⁶¹ See *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1536 (Fed. Cir. 1995) (en banc) (Newman, J., concurring) (“[T]he patent law[s] place[] strong pressure on filing the patent application early in the development of the technology, often before the commercial embodiment is developed or all the boundaries fully explored.”), *rev’d on other grounds*, 520 U.S. 17 (1997).

¹⁶² Decaire et al., *supra* note 150, at 1058.

make characterizing it difficult, even with the passage of more time.¹⁶³ In certain instances, functional language may be appropriately utilized to maximize claim scope. For example, the function of a substance may be more definite than its structure. Whether or not functional language is appropriate and utilized, preserving equivalents can better position biologics producers, as such elements might cover a biosimilar or other BLA product.¹⁶⁴

When implementing these and other strategies, a subset of considerations for at least a set of claims should focus on the specific biosimilar pathway requirements. For example, focusing on potency, purity, and safety parameters may each be valuable. Further, the current FDA draft guidelines recommend a “stepwise approach” that compares the biosimilar to the reference product with respect to several factors.¹⁶⁵ Concentrating on these factors may provide guidance on claiming strategies. Exemplary factors may include function, effectiveness, human pharmacokinetics, human pharmacodynamics, clinical immunogenicity, and related parameter.¹⁶⁶ Therefore, it would likely be beneficial to draft claims directed towards these parameters of the reference product, as well as methods of testing.

III. RESOLVING PATENT DISPUTES

A. Introduction

Given the unrelated (but intertwined) nature of the Biosimilar Act's exclusivities and the U.S. Patent Law's exclusionary rights, there will undoubtedly be patent disputes. For example, Innovators are likely to have patent coverage towards their innovator biologic products. Highly marketable innovator biologics will undoubtedly serve as a reference product for a biosimilar applicant's product. Thus, the Innovator's first reaction will be to determine whether its patent rights are infringed by the biosimilar product. Equally likely are situations in which biosimilar applicants contend that such patent rights are either not infringed by their products (or processes related to the manufacturing or testing of the product) or such rights are invalid for one or more reasons. Further, biosimilar applicants, themselves, may have patent rights that may be enforced against the Innovator. Fortunately, the Biosimilar Act anticipated such situations and has provisions that provide an avenue for resolving patent disputes.

¹⁶³ See Daron I. Freedberg, *Improvement of Biological Product Quality by Application of New Technologies to Characterize of Vaccines and Blood Products: NMR Spectroscopy and Light Scattering*, FOOD & DRUG ADMIN., <http://www.fda.gov/biologicsbloodvaccines/scienceresearch/biologicsresearchareas/ucm127270.htm> (last visited Feb. 17, 2013).

¹⁶⁴ See *supra* notes 156 and 160.

¹⁶⁵ See *supra* Part I.C.3.a.i.

¹⁶⁶ See *supra* note 45 and accompanying text.

B. Triggering of the Patent Dispute Provisions

As a preliminary matter, it is worth noting that pre-clinical and clinical investigation in preparation of regulatory filing is exempt from infringement.¹⁶⁷ This is another similarity to the European system, which also exempts pre-clinical and clinical investigations conducted in preparation for regulatory filings.¹⁶⁸ In the EU, however, the actual filing of the Marketing Authorization Application for a biosimilar product is not constructive infringement.¹⁶⁹ In the United States, the Act renders such actions constructive infringement.¹⁷⁰

The Act sets forth the process that the parties must undergo in the event of any patent disputes.¹⁷¹ The Act ensures that Innovators of the reference product are aware of any 351(k) filings.¹⁷² Specifically, a biosimilar applicant must provide its application, inclusive of details on the manufacturing process, to the Innovator of the reference product within twenty days of the FDA's acceptance for review.¹⁷³ The application is provided under confidentiality.¹⁷⁴ The Innovator then has sixty days to provide an initial list of patents that could reasonably be asserted against the biosimilar application.¹⁷⁵ As part of this process, the Innovator may optionally choose to designate patents that are available for license.¹⁷⁶

Within sixty days of receiving the initial list of the patents from the Innovator, the biosimilar applicant has the opportunity to provide an initial list of patents that it contends could reasonably be asserted by the Innovator.¹⁷⁷ For each patent that could be asserted, the biosimilar applicant can either (1) provide the Innovator with a claim chart identifying facts and law supporting invalidity, unenforceability, or non-infringement, or (2) provide a statement that the biosimilar applicant does not intend to begin marketing its product prior to the patent's expiration.¹⁷⁸ The biosimilar applicant also has the opportunity, here, to respond to the Innovator's list of patents available for licensing.¹⁷⁹ If the biosimilar applicant filed any allegations regarding non-infringement, invalidity, or unenforceability of the patents-at-issue, the Innovator has sixty days to provide rebuttals to such allegations.¹⁸⁰ Figure 1 provides a timeline of the relevant dates of the patent dispute provisions.

¹⁶⁷ 35 U.S.C. § 271(e)(1) (2012).

¹⁶⁸ See Patents Act, 1977, c. 37, § 60(5) (U.K.).

¹⁶⁹ See Loeb, *supra* note 140 (comparing U.S. and European biosimilar regulation and litigation).

¹⁷⁰ 35 U.S.C. § 271(e)(2)(C).

¹⁷¹ 42 U.S.C. § 262(l)(4)–(7).

¹⁷² See, e.g., *id.* § 262(l)(3) (requiring subsection (k) applicants and reference product sponsors to exchange lists of patents implicated).

¹⁷³ *Id.* § 262(l)(2).

¹⁷⁴ *Id.* § 262(l)(1)(B).

¹⁷⁵ *Id.* § 262(l)(3)(A)(i).

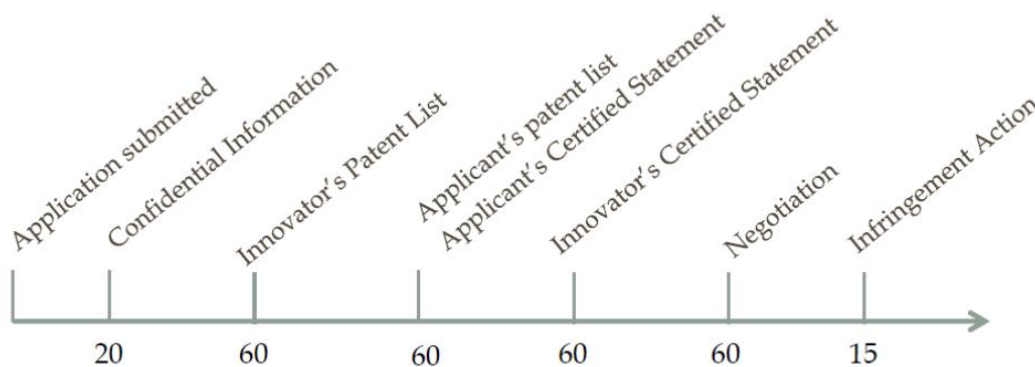
¹⁷⁶ *Id.* § 262(l)(3)(A)(ii).

¹⁷⁷ *Id.* § 262(l)(3)(B)(i).

¹⁷⁸ *Id.* § 262(l)(3)(B)(ii).

¹⁷⁹ *Id.* § 262(l)(3)(B)(i).

¹⁸⁰ *Id.* § 262(l)(3)(C).

Figure 1. Timeline of the Patent Dispute Provisions*C. Negotiating the Basis for an Infringement Action*

At this point, the parties have fifteen days to negotiate a list of patents to form the basis for an infringement action.¹⁸¹ The Act contemplates the fact that some negotiations are likely to be more contentious than others and, as such, recognizes that the parties may not reach an agreement.¹⁸² If there is not an agreement, then the Act's patent exchange procedures are triggered in which a biosimilar applicant identifies the number of patents it will exchange.¹⁸³ Under this scenario, the biosimilar applicant controls the number of patents in an infringement action.¹⁸⁴ Specifically, the Innovator cannot list a number of patents greater than the number identified by the biosimilar applicant.¹⁸⁵ An exception exists when the biosimilar applicant identifies zero patents in which the Innovator can list one patent.¹⁸⁶ Within five days, the parties simultaneously exchange lists of patents.¹⁸⁷ The Innovator then has thirty days to bring an infringement action for each patent on both lists.¹⁸⁸

Alternatively, if the parties negotiate a list of patents to form the basis for an infringement action, the Innovator has the thirty days to bring an infringement action for each of the negotiated patents.¹⁸⁹ Upon filing of the patent infringement action, the biosimilar applicant provides notice to the FDA, and the FDA publishes notice of complaint in the Federal Register.¹⁹⁰ The FDA does not suspend review of

¹⁸¹ *Id.* § 262(l)(4)(B).

¹⁸² *Id.*

¹⁸³ *Id.* § 262(l)(5)(B)(i).

¹⁸⁴ *Id.*

¹⁸⁵ *Id.* § 262(l)(5)(B)(ii)(I).

¹⁸⁶ *Id.* § 262(l)(5)(B)(ii)(II).

¹⁸⁷ *Id.* § 262(l)(5)(B)(i)(I).

¹⁸⁸ *Id.* § 262(l)(6)(B).

¹⁸⁹ *Id.* § 262(l)(6)(A).

¹⁹⁰ *Id.* § 262(l)(6)(C).

the abbreviated application as a result of a potential patent dispute.¹⁹¹ This is unlike the Hatch-Waxman Act in which the Innovator must list their patents in the Orange Book, and the FDA review is suspended for thirty months if an Innovator files suit.¹⁹²

1. Preliminary Injunction Procedures

The Act further contemplates that a patent may issue after the Innovator provides its initial list of patents.¹⁹³ For patents that are issued or licensed after the Innovator identifies its initial list, the Innovator will supplement the initial list with the additional patents within thirty days.¹⁹⁴ The biosimilar applicant then has thirty days to provide a position on non-infringement, invalidity, or unenforceability.¹⁹⁵ It should be noted, however, that these patents are not part of the negotiated/exchange procedures, but are instead subject to Preliminary Injunction procedures.

The Act requires that the biosimilar applicant provide the Innovator with a 180-day notice of intent to market.¹⁹⁶ The Innovator may seek a preliminary injunction (“PI”) on any patents on any lists.¹⁹⁷ The biosimilar applicant must reasonably cooperate to expedite discovery in any infringement action by the Innovator seeking PI.¹⁹⁸

2. Declaratory Judgments

With respect to seeking a declaratory judgment (“DJ”), the Act limits a DJ action.¹⁹⁹ In particular, if the Innovator had confidential access to the biosimilar application, neither party can bring a DJ action before the 180-day notice of commercial marketing is received.²⁰⁰ Moreover, DJ actions can only be brought against patents for which a PI motion has been filed.²⁰¹ Importantly, if the biosimilar applicant fails to respond during the process described above, the Innovator can bring a DJ action on any patent on the Innovator’s initial list and list of newly issued/licensed patents.²⁰² If the biosimilar applicant fails to provide access to confidential information during the patent dispute process, the Innovator can bring a DJ action on any patent that claims the biological product or its use, but *not* that claims manufacture of the biological product.²⁰³

¹⁹¹ See Lisa H. Wang, *Biosimilar Act Differs from Hatch-Waxman in Several Key Ways*, GIBBONS LAW (Aug. 16, 2010), <http://www.gibbonslaw.com/UserFiles/Image/1288801911.pdf>.

¹⁹² See 21 C.F.R. § 314.107(b)(3)(i)(A) (2013).

¹⁹³ 42 U.S.C. § 262(l)(7) (2012).

¹⁹⁴ *Id.*

¹⁹⁵ *Id.*

¹⁹⁶ *Id.* § 262(l)(8)(A).

¹⁹⁷ *Id.* § 262(l)(8)(B).

¹⁹⁸ *Id.* § 262(l)(8)(C).

¹⁹⁹ *Id.* § 262(l)(9).

²⁰⁰ *Id.* § 262(l)(9)(A).

²⁰¹ *Id.*

²⁰² *Id.* § 262(l)(9)(B).

²⁰³ *Id.* § 262(l)(9)(C).

CONCLUSIONS

In view of the patent dispute provisions of the Act, an Innovator should make sure to identify ALL of the patents that are a potential interest for litigation because, if any are left off of the list and the biosimilar applicant does not identify them, then the Innovator cannot sue on such patents prior to launch.²⁰⁴ The only exception would be in the situation where the biosimilar applicant fails to provide confidential access during the patent dispute process.²⁰⁵ Patents identified on negotiated or exchanged lists, however, can be litigated immediately.²⁰⁶ Patents on the Innovator's initial list, but not on negotiated or exchanged lists, cannot be litigated until a 180-day marketing notice is provided.

²⁰⁴ *Id.* § 262(l)(6)(A).

²⁰⁵ *Id.* § 262(l)(9)(C).

²⁰⁶ *Id.* § 262(l)(9)(A)–(B).