

Foreward

Follow-On Biologics: Implementation Challenges and Opportunities

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This Book of the *Seton Hall Law Review* presents the contributions to *Follow-On Biologics: Implementation Challenges and Opportunities*, a one-day roundtable event hosted by Seton Hall University School of Law in the fall of 2010.¹ The roundtable fostered an international dialogue regarding the future of follow-on biologics in the United States resulting from the Patient Protection and Affordable Care Act of March 2010.

I. THE BIOLOGIC PRICE COMPETITION AND INNOVATION ACT OF 2010

The March 23, 2010, enactment of the Patient Protection and Affordable Care Act (PPACA)² and the companion Health Care and Education Affordability Reconciliation Act of 2010³ ushered in landmark reform of the American health care system. Along with sweeping overhauls of the health care system generally, PPACA also provides a new regulatory challenge for the Food and Drug Administration (FDA). A subtitle within PPACA, the Biologics Price Competition and Innovation Act (BPCIA),⁴ bestows upon FDA broad authority to implement an abbreviated approval route to market for

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¹ The roundtable was co-sponsored by the Gibbons Institute for Law, Science & Technology and the Center for Health & Pharmaceutical Law & Policy at Seton Hall University School of Law. The author would like to thank all roundtable presenters and participants for contributing to the event and to particularly thank Donna M. Gitter and Henry Grabowski (and co-authors) for developing full-length Articles for this Book of the *Seton Hall Law Review*.

² Pub. L. No. 111-148, 124 Stat. 119 (2010) (codified in scattered sections of 21 U.S.C., 35 U.S.C., and 42 U.S.C.).

³ Pub. L. No. 111-152, 124 Stat. 1029 (2010).

⁴ Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001-03, 124 Stat. 119, 804-21 (2010) [hereinafter BPCIA].

biological products (also known as biologics) that are “biosimilar” to an existing marketed product.⁵

This brief introduction will provide a basic comparison of biologics and conventional pharmaceutical drugs that will prove central to the FDA’s development of this follow-on biologic pathway as well as specifically examine the content and scope of the BPCIA provisions and identify future challenges for the FDA. It will conclude by highlighting details of presentations during the roundtable held at the Seton Hall University School of Law and introduce the two resulting articles contained within this Book of the *Seton Hall Law Review*.⁶

II. COMPARING BIOLOGICS AND PHARMACEUTICAL DRUGS

Biologics are medical products derived from living sources (animals, humans, and microorganisms) and include viruses, therapeutic serums, toxins and antitoxins, vaccines, blood and blood products, and cells, tissues and gene therapy products.⁷ As described by the FDA, biological products are divided into a number of categories: allergenics, including allergen patch tests and allergenic extracts; blood and blood products, including blood, blood components, blood bank devices, and blood donor screening tests; cellular and gene therapy products, including gene-based and cell-based treatments; tissue and tissue products, including bone, skin, corneas, ligaments, tendons, and stem cells; vaccines; and xenotransplantation (transplantation of non-human cells, tissues, or organs).⁸

⁵ 42 U.S.C. § 262(i)(1) (Supp. IV 2010). The new follow-on biologics provisions create statutory mechanisms to provide for approval of a biological product that is “biosimilar” and/or “interchangeable” with a biologic reference product already on the market. § 262(i)(3). This status is to be based on whether a follow-on product is “highly similar” to the reference product. § 262(i)(2).

⁶ Henry Grabowski, Genia Long & Richard Mortimer, *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511 (2011); Donna M. Gitter, *Informed by the European Union Experience: What the United States Can Anticipate and Learn from the European Union’s Regulatory Approach to Biosimilars*, 41 SETON HALL L. REV. 559 (2011).

⁷ § 262(i). A biological product is defined 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 to the prevention, treatment, or cure of a disease or condition of human beings.

Id.

⁸ *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm> (last visited Jan. 30, 2011).

Biologics differ from traditional pharmaceutical drugs in a number of ways—aside from their origination from living rather than chemically synthesized sources, they are also more complex macromolecular entities, they are typically manufactured using more sophisticated techniques, and they are more susceptible to variations in final product given manufacturing and storage conditions. Biologics consist of proteins whose structure is determined by four organizational levels: their amino acid sequence, their spatial configuration, any three-dimensional folding that occurs, and their interactions.⁹ The final product is largely dependent on manufacturing process used and there can be variation in biological activity due to media, temperature, and other interactions.¹⁰ Approval is achieved through either the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (CDER) depending on product type.¹¹ The statutory authority for approval lies in the Public Health Services Act (PHSA).¹²

Conventional pharmaceutical drugs, on the other hand, are small molecules that are chemically synthesized and relatively simple to characterize compared to biologics.¹³ They are approved through the New Drug Application (NDA) process overseen by CDER after proving safety and efficacy and fulfilling all other substantive requirements of the Food, Drug and Cosmetic Act (FDCA).¹⁴ Two abbreviated routes to market exist for new drugs within the FDCA—one of which is the generic route to market, or the Abbreviated New Drug Application (ANDA).¹⁵ In 1997, the Food and Drug Administration

⁹ See JUDITH A. JOHNSON, CONG. RESEARCH SERV., FDA REGULATION OF FOLLOW-ON BIOLOGICS 10 (Apr. 26, 2010), available at http://www.primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.pdf.

¹⁰ *Id.*

¹¹ *About the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/CDER/default.htm> (last visited Jan. 30, 2011); *Center for Biologics Evaluation and Research (CBER) Responsibilities Questions and Answers*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133072.htm> (last visited Jan. 30, 2011).

¹² 42 U.S.C. § 262(a) (Supp. IV 2010).

¹³ See JOHNSON, *supra* note 9, at Summ.

¹⁴ See Food, Drug and Cosmetic Act (FDCA), Pub. L. 75-717, § 505(b), 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 355(b) (Supp. IV 2010)); *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm> (last visited Jan. 30, 2011).

¹⁵ These two routes are the ANDA and the § 505(b)(2) process set out in FDCA § 505(j) and § 505(b)(2). 21 U.S.C. §§ 355(j), 355(b)(2). Over the counter (OTC) drugs adhering to an OTC Monograph can enter the market without the new drug

Modernization Act amended both the PHSA and FDCA to create uniformity in the NDA and Biologics License Application (BLA) approval processes, yet they remain under separate statutory authority.¹⁶ A BLA is issued by the FDA after finding that the product is safe, pure, and potent and that the manufacturing facility assures this;¹⁷ it thus incorporates classic FDCA provisions and structures of investigational new drug applications (INDs) for initiation and progress of clinical trials and similar measures of safety and efficacy of NDAs, including good manufacturing practices and post-market mechanisms.

Despite the parallels in the NDA approval process for pharmaceutical drugs¹⁸ and the BLA approval process for biologics,¹⁹ the statutory and regulatory mechanisms permitting generic approval, market exclusivity and patent exclusivity provisions did not previously exist for biologics due to the bifurcated statutory authority—the drug approval process residing in the FDCA and the biologics approval pathway residing in the PHSA. Previous implementation of the ANDA (generic drug) process amended the FDCA, not the PHSA, and thus the abbreviated approval pathway and accompanying patent and exclusivity provisions of the Hatch-Waxman Act of 1984 did not cover biologics.²⁰ The core requirement for generic drug sponsors utilizing the ANDA route is to show “bioequivalence” to the pioneer drug based on comparison studies rather than extensive clinical trials

process, as they are regarded as “generally recognized as safe and effective.” 21 CFR 330.1 (2010).

¹⁶ See Food and Drug Administration Modernization Act (FDAMA) of 1997, Pub. L. 105-115, § 112, 111 Stat. 2296.

¹⁷ 42 U.S.C. § 262(a)(2)(C)(i) (Supp. IV 2010).

¹⁸ A drug is defined as:

(A) articles recognized in the official U.S. Pharmacopeia, . . . and (b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (c) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (d) articles intended for use as a component

FDCA § 201(g)(1). A new drug is defined as:

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling

§ 201(p)(1).

¹⁹ 42 U.S.C. § 262 (Supp. IV 2010).

²⁰ See FDCA, Pub. L. 75-717, § 505(j). This legislation implemented the generic drug approval process and related exclusivity incentives. *Id.*

showing safety and efficacy required in the NDA process.²¹ The ANDA process allows a generic drug sponsor to enter the market subject to certain patent certifications that directly assert that a pioneer drug is invalid or unenforceable.²² The first successful generic sponsor to assert such a certification in their ANDA application receives 180 days of exclusivity during which another generic version cannot enter the market.²³

The lack of an abbreviated approval process for biologics prior to the BPCIA has assured pioneer biologics a long term of patent protection and financial profit. The Federal Trade Commission reports that in 2007 alone Americans spent \$40.3 billion on biologics (out of a total \$286.5 billion for prescription drugs), with an individual cost of common treatments for rheumatoid arthritis and breast cancer costing patients \$20,000 and \$48,000 per year, respectively.²⁴ A *New York Times* Op-Ed offers that some biologics exceed \$200,000 per year.²⁵ That same article reports that biologics, on average, cost twenty-two times that of ordinary drugs and that the six top-selling biologics make up 43% of the Medicare Part B drug budget.²⁶ Given that the first generic pharmaceutical drug to enter the market generally offers a price discount 25% lower than pioneer (rising to 80% price discount with multiple generics on the market),²⁷ the hope is that a follow-on biologics pathway will provide similar savings.

III. CONCEPTS OF “BIOSIMILARITY”

Driven largely by the decades-long debate on the rising costs of biologics, the BPCIA is aimed at curbing these costs both to consumers and federal reimbursement schemes by creating a generic-like route to market for biosimilar biological products.²⁸ The BPCIA

²¹ § 505(j)(2)(A)(iv).

²² § 505(j)(2)(A)(i)–(viii).

²³ § 505(j)(2)(A)(iii)–(iv).

²⁴ FED. TRADE COMM’N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, at i (2009) [hereinafter FTC REPORT], available at <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf>. The report provides that patients pay \$20,000/year for Remicade (for treatment of Rheumatoid arthritis) and \$48,000/year for Herceptin (for treatment of breast cancer). *Id.*

²⁵ Anthony D. So & Samuel L. Katz, Op-Ed, *Biologics Boondoggle*, N.Y. TIMES, Mar. 8, 2010, at A23. This article reports that patients pay \$200,000/year for Cerezyme (for treatment of Gaucher disease). *Id.*

²⁶ *Id.*

²⁷ FTC REPORT, *supra* note 24, at 12.

²⁸ See *Implementation of the Biologics Price Competition and Innovation Act of 2009*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm> (last visited Feb. 2, 2011). Some argue fol-

creates an approval pathway for submission of a BLA for a “biosimilar” and/or “interchangeable” biologic.²⁹ Biosimilarity is defined within the legislation to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and “there are no clinically meaningful differences between the biological product and the reference product in terms of . . . safety, purity, and potency.”³⁰ Interchangeability is defined to mean that the requirements for “biosimilarity” are fulfilled and the biological product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”³¹

While the specific details of the new process have been left to the FDA, Congress provided some general guidance. The biosimilarity BLA application content must include analytical studies, animal studies, and a clinical study or studies with the following requirements: they must have the same mechanism(s) of action for condition(s) of use that “have been previously approved for the reference product”: they must have the same route of administration, dosage form, and strength; and the facility must assure the development of a safe, pure, and potent product.³² However, the legislation also specifically gives FDA discretion to decide requirements on a case-by-case basis.³³ For a finding of interchangeability, the BLA application content must be biosimilar *plus* include a showing of the expectation to provide the same clinical result as the reference product in any given patient³⁴ and a showing that where “administered more than once to an individual, the risk in terms of safety of diminished efficacy of alternating or switching between use of the biological product and the

low-on biologics should not be referred to as “generic” biologics due to the differences in characteristics described above. See Susan Aldridge, *Why Biosimilars Are Not True Generics*, PHARMACEUTICAL TECHNOLOGY EUROPE, June 1, 2007, <http://pharmtech.findpharma.com/pharmtech/Biopharmaceuticals/Why-biosimilars-are-not-true-generics/ArticleStandard/Article/detail/435320>. The phrase “highly similar” as laid out in the BPCIA is not the same as “bioequivalence” as utilized in generic determinations. Federal regulations define bioequivalence as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” 21 C.F.R. § 320.1(e) (2010).

²⁹ 42 U.S.C. § 262(i)(1) (Supp. IV 2010).

³⁰ § 262(i)(2).

³¹ § 262(i)(3).

³² § 262(k)(2)(A)(i).

³³ § 262(k)(2)(A)(ii).

³⁴ § 262(k)(3).

reference product is not greater than the risk of using the reference product without such alternation or switch.”³⁵

The BPCIA sets out to accomplish the development of the follow-on biologic provisions through several key mechanisms. First, the Secretary of the Department of Health and Human Services, partnering with the Commissioner of the FDA, is authorized to issue “guidance” regarding standards and criteria and implement approval processes utilizing public comment.³⁶ The BPCIA also creates a process for the resolution of patent disputes, including disclosure requirements for biosimilar applicants to the pioneer biologic and an ensuing back and forth system of patent status and litigation assessment.³⁷ There are a number of incentives to encourage follow-on development, including a twelve-year period of market exclusivity for pioneer biologics,³⁸ a one-year period of exclusivity for the first product deemed “interchangeable” to a pioneer biologic,³⁹ and an additional six months of exclusivity for pediatric studies.⁴⁰ However, the exact type of exclusivity available under the BPCIA is currently open for debate. In public notifications and requests for comment, the FDA has interpreted the language of the BPCIA to provide for 12 years of market exclusivity, while some members of Congress and industry argue that it provides either for 12 years of data exclusivity or four years of data exclusivity followed by eight years of market exclusivity.⁴¹ Specifically, the statute provides that applications “may not be submitted to the Secretary until the date that is four years after the date on which the reference product was first licensed” and that approval “may not be made effective . . . until the date that is 12 years after the date on which the reference product was first licensed.”⁴²

Aside from deciphering the expansive legislative language contained within the BPCIA, core challenges for the FDA will be determining appropriate scientific and technical measures for comparison between the pioneer biologic and the “biosimilar” product, selecting how to implement regulatory mechanisms and procedures (either

³⁵ 42 U.S.C. § 262(k)(4)(A)–(B) (Supp. IV 2010).

³⁶ § 262(k)(8).

³⁷ § 262(l).

³⁸ § 262(k)(7)(A).

³⁹ § 262(k)(6)(A).

⁴⁰ § 262(m)(2)(A).

⁴¹ Alicia Mundy, *Firms Push for Biotech Generics*, WALL ST. J., Jan. 26, 2011, <http://online.wsj.com/article/SB10001424052748704013604576104413760150024.html>; Derrick Gingery, *Biosimilars Exclusivity Tug-of-War Brewing in the Mail; Can a Letter Add Eight Years to Reviews?*, PINK SHEET, Jan. 31, 2011, at 9.

⁴² PHSA, §351(k)(7)(A)–(C) (2010) (codified at 42 U.S.C. §262(k)(7)(A)–(C)).

through rulemaking, guidance documents, or on a case-by-case basis), and navigating its role in the novel patent and exclusivity provisions.

IV. SETON HALL UNIVERSITY SCHOOL OF LAW ROUNDTABLE

On October 29, 2010, Seton Hall University School of Law hosted a roundtable event addressing the BPCIA provisions and the future of the new biosimilar pathway, entitled “Follow-On Biologics: Implementation Challenges and Opportunities.” Roundtable participants represented a range of perspectives and professional disciplines spanning law, science, health, economics, and public policy. The event examined the current legal status of follow-on biologics, specifically exploring the legislative provisions; scientific and regulatory distinctions between the established generic drug approval processes and the new yet to be determined approval process for follow-on biologics, focusing on differences between traditional pharmaceutical drugs and biologics based on size, characteristics, complexity, manufacturing processes, reproducibility, and concepts of similarity and interchangeability; comparisons of the BPCIA with international oversight of follow-on biologics in the European Union; market and patent exclusivity concerns, particularly Hatch-Waxman issues; and overarching concerns for industry and consumers.

National and international experts kicked off the event with plenary presentations on various aspects of the legislation that promise to pose challenges to the existing oversight regime for biological products in the United States. In order to frame the discussion, Dr. Falk Ehmann, M.D., Ph.D., M.Sc. (Scientific Secretariat of the European Medicines Agency’s Biosimilar Working Party; Safety & Efficacy of Medicines Sector, Human Medicines Development and Evaluation Unit), presented on “Biosimilars in the European Union: From Legislation to Future Challenges—Experiences and Perspectives.” He highlighted the core implementation mechanisms, current scientific questions, and future goals for the European Union, which has had a follow-on biologic pathway since 2005. Suzanne Drennon Munck, J.D. (Counsel for Intellectual Property for the Federal Trade Commission), spoke on the topic of “Follow-On Biologics: A Federal Trade Commission Perspective,” providing background on FTC activity and its position on the follow-on pathway to market, focusing on her own perspective of barriers to competition introduced with the patent resolution process and patent exclusivity periods in the new legislation. Dr. Henry Grabowski, Ph.D. (Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics at

Duke University), discussed “Implementation of the Biosimilar Pathway: Economic and Policy Issues,” offering an economic analysis of the effects of the new follow-on provisions, specifically examining health care cost savings and innovation incentive aspects of the BPCIA’s data and patent exclusivity provisions.

The afternoon consisted of a traditional roundtable format, allotting time to seven expert panelists to present among colleagues and actively discuss particular aspects of the follow-on provisions with both the morning plenary presenters and the audience. Jill Deal, J.D. (Partner at Venable LLP), forecasted FDA moves using generic Enoxapirin (Lovenox®) as a case study.⁴³ Phil Katz, J.D. (Partner and Practice Area Leader of Pharmaceuticals & Biotechnology at Hogan Lovells), examined current FDA activity and future concerns confronted by the FDA in implementing the new legislation.⁴⁴ Dr. William M. Egan, Ph.D. (Vice President of PharmaNet Consulting), discussed a variety of technical and scientific questions regarding “highly similar” measures and “interchangeability” including adequacy of international naming standards.⁴⁵ Reza Green, Ph.D., J.D. (Chief Intellectual Property Counsel of Novo Nordisk), examined the back-and-forth patent disclosure mechanisms in the BPCIA, discussing difficulties for both the pioneer biologic and the follow-on biologic sponsor in the areas of confidentiality, pre-litigation admissions, and pre-existing licensing agreements.⁴⁶ Chris Holman, Ph.D., J.D. (Associate Professor of Law at the University of Missouri-Kansas City School of Law), assessed the landscape of biologic patents, comparing and contrasting them with patents for conventional pharmaceutical drugs.⁴⁷ Nathan Cortez, J.D. (Assistant Professor of Law at Southern Methodist University Dedman School of Law), mapped the international legal authority for post-marketing and pharmacovigilance for follow-on biologics in the European Union, Japan, and Canada.⁴⁸ Donna Gitter, J.D. (Associate Professor of Law at Baruch College, The City Uni-

⁴³ The presentation was entitled “Where is FDA Likely to Go: Enoxapirin Sodium (Lovenox®) as a Possible Case Study.”

⁴⁴ The presentation was entitled “Open Issues Confronted by FDA.”

⁴⁵ The presentation was entitled “Biosimilars, Interchangeable Biosimilars, and the U.S. Legislation.”

⁴⁶ The presentation was entitled “The Patent Dance: Follow-On Biologics Patent Disclosure Process.”

⁴⁷ The presentation was entitled “The Role of Patents in Maintaining Market Exclusivity for Biologics.”

⁴⁸ The presentation was entitled “Charting the Global Trend towards Biosimilars.”

versity of New York), identified lessons for the United States gleaned from the European Union experience.⁴⁹

The following two full-length Articles result from the roundtable experience: Henry Grabowski, Genia Long, and Richard Mortimer, "Implementation of the Biosimilar Pathway: Economic and Policy Issues,"⁵⁰ and Donna M. Gitter, "Informed by the European Union Experience: What the United States Can Anticipate and Learn from the European Union's Regulatory Approach to Biosimilars."⁵¹

⁴⁹ The presentation was entitled "Informed by the European Union Experience: What the United States Can Anticipate and Learn from the European Union's Regulatory Approach to Biosimilars."

⁵⁰ See Grabowski et al., *supra* note 6.

⁵¹ See Gitter, *supra* note 6.