

Implementation of the Biosimilar Pathway: Economic and Policy Issues

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I. INTRODUCTION

The Biologics Price Competition and Innovation Act of 2009 (BPCIA), enacted as part of the Patient Protection and Affordable Care Act of 2010 (PPACA), created an abbreviated pathway for the FDA to approve biosimilars.¹ This legislation broadly complements the twenty-five-year-old Drug Price Competition and Patent Term Restoration Act of 1984 (generally referred to as the Hatch-Waxman Act),² which provides a clear path for generic drug entry in the case of new chemical entities (NCEs) approved under the Food, Drug, and Cosmetic Act (FD&C Act)³ through the Abbreviated New Drug Application (ANDA) process.⁴ Through the ANDA process, generic drugs demonstrated to be bioequivalent to off-patent reference drugs may be approved without the submission of clinical-trial data.⁵ The Hatch-Waxman Act, however, does not apply to most large-molecule biologic medicines, which generally are regulated under the Public Health Service Act and had no corresponding provision to the ANDA prior to passage of the BPCIA.⁶ Although some biologics were approved under the FD&C Act for historical reasons, and therefore already exposed to potential generic competition, most biotech drugs

¹ Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, § 7001-03, 124 Stat. 119, 804-21 (2010) [hereinafter BPCIA]. Applications under this pathway are to demonstrate that “the biological product is biosimilar to the reference product,” utilizing the same mechanism(s) of action as the reference product (if known), and is to be used for the same condition(s) with the same route of administration, dose, and strength as the reference product. § 7002.

² Pub. L. No. 98-417, 98 Stat. 1585.

³ Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended in 21 U.S.C. § 355 (Supp. IV 2010)).

⁴ 21 U.S.C. §§ 355(j).

⁵ To obtain approval of an ANDA, manufacturers must establish that the generic drug product is bioequivalent to the reference drug and has the same active ingredient(s), route of administration, dosage form, strength, previously approved conditions of use, and labeling (with some exceptions). § 355(j)(2)(A). Bioequivalence is defined 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” (with some exceptions). 21 C.F.R. § 320.1 (2010). For bioequivalence to be established, the pharmacokinetic studies should find that the generic product is within a confidence interval of 80% to 125% of the branded drug in terms of bioequivalence (a non-binding recommendation). U.S. DEP’T OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS 20 (2003), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>.

⁶ See 42 U.S.C. § 262 (Supp. IV 2010).

will face competition from products coming to market through an expedited approval process—relying at least in part on the innovator’s package of data and/or a prior FDA approval for the first time as a result of the BPCIA.⁷

Some of the key provisions of the new legislation are:

Similarity and Interchangeability: A biosimilar does not have to be chemically identical to its reference product, but there must be “no clinically meaningful differences . . . in terms of safety, purity, and potency.”⁸ The FDA can find that a biosimilar is interchangeable with its reference product if it can be shown that switching between the products produces no additional risk in terms of safety or efficacy beyond that posed by the reference product alone.⁹ The first biosimilar shown to be interchangeable is entitled to a one-year exclusivity period during which no other product may be deemed interchangeable with the same reference product.¹⁰

Regulatory Review: The FDA will determine whether a product is biosimilar to a reference product based on analytical, animal-based, and clinical studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics).¹¹ The FDA may waive the need for any of these studies in individual cases.¹² The FDA may, but is not required to, conduct rulemaking or issue guidance before reviewing or approving a specific application.¹³ It may also conclude that based on the state of science and experience, biosimilars to certain products or in a certain class of products will not be approved.¹⁴

⁷ The FDA’s review and eventual approval of two “biosimilar-like” applications were both for products approved under the FD&C Act: an ANDA for enoxaparin sodium, referencing Sanofi-Aventis’s Lovenox, and a § 505(b)(2) application for Omnitrope. See *infra* Part III.A.

⁸ 42 U.S.C. § 262(i)(2)(B) (Supp. IV 2010).

⁹ § 262(i)(3).

¹⁰ § 262(k)(6). Other litigation-related provisions apply. Exclusivity is the earliest of: one year after the first commercial marketing for the first-approved biosimilar found to be interchangeable; or 18 months after a final court decision, including appeal on all patents in a suit against the first interchangeable biologic, or the dismissal of a suit against the first interchangeable biologic; or 42 months after the approval of the first interchangeable biologic if litigation is still ongoing; or 18 months after approval of the first interchangeable biologic if the applicant has not been sued. *Id.*

¹¹ § 262(k)(2)(A)(i)(I).

¹² § 262(k)(2)(A)(ii).

¹³ § 262(k)(8). The FDA may issue general or class-specific standards or guidelines (as the European Medicines Agency does) after a public comment period, but it is not required to do so. *Id.* If the FDA issues guidelines, it must include the criteria it will use to determine interchangeability and similarity. *Id.*

¹⁴ § 262(k)(8)(E).

Exclusivity for the Innovative Biologic: Biosimilar applications may be submitted beginning four years after FDA approval of the reference innovative product.¹⁵ Before the FDA can approve a biosimilar using the abbreviated pathway, however, there is a twelve-year period of exclusivity following FDA approval of the innovative biologic.¹⁶ An additional six months of exclusivity is available for the reference innovative biologic if pediatric-study requirements are met, which applies to both the four- and twelve-year exclusivity periods.¹⁷ There has been controversy surrounding the most appropriate terminology for these provisions and discussion regarding the Congressional intent of the innovator biologic exclusivity periods in the BPCIA. Therefore, in this Article, we refer to the four-year, twelve-year, and six-month exclusivity periods defined in the statute collectively, simply as new-biologic-entity exclusivity (NBE exclusivity) and to new innovative (rather than interchangeable or biosimilar) biologics as NBEs.¹⁸

Anti-Evergreening Provisions: Several types of licensures or approvals are not eligible for NBE exclusivity, including: (1) a supplemental biologics license application (sBLA) for the reference biologic product; (2) a subsequent BLA filed by the same sponsor, manufacturer, or other related entity as the reference biologic product that does not include structural changes in a biologic's formulation (i.e., a new indication, route of administration, dosing schedule, dosage form, deli-

¹⁵ § 262(k)(7)(B).

¹⁶ § 262(k)(7)(A).

¹⁷ § 262(m).

¹⁸ In a recent letter to the FDA, members of Congress noted that these provisions should be distinguished from and do not offer "market exclusivity for innovator products," which would "prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a similar or competitive product." Letter from Representatives Anna Eshoo, Jay Inslee & Joe Barton, U.S. House of Representatives, to the Food & Drug Admin. (Dec. 21, 2010), *available at* <http://www.hpm.com/pdf/EIB%20Ltr%20FDA%20DEC%202010.pdf>. A letter using similar language was submitted by several senators, stating that "It (the Act) does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a full biologics license application rather than an abbreviated application that relies on the prior approval of a reference product." Letter from Senators Kay Hagan, Orrin Hatch, Michael Enzi & John Kerry, U.S. Senate, to Dr. Margaret Hamburg, Comm'r, Food & Drug Admin. (Jan. 7, 2011), *available at* <http://www.hpm.com/pdf/1-7-11%20Senate%20Biologics%20letter%20to%20FDA.pdf>. A third letter was submitted to the FDA by several other senators, noting their opposition to "statutory interpretations which, if implemented by the FDA, could result in generic competition being delayed well beyond the 12 year exclusivity period in statute." Letter from Senators Sherrod Brown, John McCain, Charles Schumer & Tom Harkin, U.S. Senate, to Dr. Margaret Hamburg, Comm'r, Food & Drug Admin., (Jan. 24, 2011), *available at* <http://www.hpm.com/pdf/1-24-11%20BPCIA%20Excl%20Letter%20to%20Hamburg.pdf>.

very system, delivery device, or strength); or (3) a subsequent BLA filed by the same sponsor, manufacturer, or other related entity as the reference biologic product and reflecting structural changes in a biologic's formulation that does not result in improved safety, purity, or potency.¹⁹

Reimbursement: A potential disincentive for biosimilar adoption is mitigated by setting the reimbursement for a biosimilar under Medicare Part B at the sum of its Average Selling Price (ASP) and six percent of the ASP of the biological reference product.²⁰

Patent Provisions: The BPCIA requires a series of potentially complex private information exchanges among the biosimilar applicant, reference product sponsor, and patent owners, followed by negotiations and litigation, if necessary.²¹ In contrast to the patent provisions for new chemical entities under the Hatch-Waxman Act, there is no public listing akin to the Orange Book, no thirty-month stay when a patent infringement suit is brought, and no 180-day exclusivity awarded to the first firm to file an abbreviated application and achieve a successful Paragraph IV patent challenge.²²

In this Article, we consider a number of demand- and supply-side economic factors that will affect how competition between branded biologics and biosimilars may evolve over the foreseeable future. These factors are based on current market dynamics, the provisions of the new law, initial European biosimilar experience, and experience under the Hatch-Waxman Act, taking into account differences between biologics and chemically-synthesized drugs and between the two regulatory frameworks.

Biologics are typically more complex molecules than small-molecule chemical drugs. They are not manufactured through clinical synthesis but instead, are produced through biological processes involving manipulation of genetic material and large-scale cultures of living cells, where even small changes to the manufacturing process can lead to significant changes in safety and efficacy.²³ As a result, establishing that a biosimilar is "similar enough" to achieve comparable therapeutic effects in patients is a much more challenging task for

¹⁹ § 262(k)(7)(C).

²⁰ *Id.* § 1395w-3a(b)(8).

²¹ *Id.* § 262(l).

²² *Id.* § 355(j); see also 21 C.F.R. § 314.107(b)(3)(i)(A) (2010).

²³ See Henry Grabowski et al., *The Market for Follow-on Biologics: How Will it Evolve?*, 25 HEALTH AFFS. 1291, 1291–1301 (2006).

companies and regulators than establishing bioequivalence for generic chemical entities.²⁴

FDA regulatory requirements for biosimilar approval will affect the investment necessary to gain market approval, the number of potential competitors, and how competition will evolve in terms of both price and product differentiation.²⁵ Other important factors influencing market competition include reimbursement for, and access to, biosimilars by government and private insurers, as well as patent disclosure and resolution provisions, and future intellectual property litigation.²⁶ NBE exclusivity provisions in the new Act will have a long-term impact on incentives for investment in innovation and the development of new biologic therapies.²⁷ As with any new legislation, a

²⁴ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Subcomm. on Health, and H. Comm. on Energy and Commerce*, 110th Cong. 22 (2007) (statement of Janet Woodcock, M.D., Deputy Comm'r, Chief Med. Officer, FDA), available at <http://www.fda.gov/NewsEvents/Testimony/ucm154017.htm>; Asher Mullard, *Hearing Shines Spotlight on Biosimilar Controversies*, 9 NAT. REVS. DRUG DISCOVERY 905, 905–06 (2010). On the one hand, subtle changes in manufacturing have resulted in changes in the characteristics of finished product: Raptiva produced according to the same protocol by Genentech, and its partner XOMA exhibited different pharmacokinetic profiles; Genzyme's scale-up for Myozyme from 160 liters to a 2,000 liter production capacity was associated with glycosylation profile changes, resulting in a separate BLA requirement for the 2,000 liter product; the introduction of an uncoated rubber stopper in the prefilled syringes for Eporex is thought to have been associated with a number of cases of red blood cell aplasia. See, e.g., Katia Boven et al., *The Increased Incidence of Pure Red Cell Aplasia with an Eporex Formulation in Uncoated Rubber Stopper Syringes*, 67 KIDNEY INT'L 2346 (2005) (scientific study finding that the use of rubber syringe stoppers was associated with an increased incidence of pure red cell aplasia with Eporex); *Genentech and XOMA Obtain Results from Xanelim™ (Efalizumab) Pharmacokinetic Study*, GENENTECH (Apr. 5, 2002), <http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=4947>; *Myozyme Produced at the 2000 L Bioreactor Scale to Receive Accelerated Approval*, UNITED POMPE FOUNDATION (Feb. 28, 2009), http://www.unitedpompe.com/articles2.cfm?Article_Selected=528. Others have cited Amgen's change in manufacturing process from the previous "roller ball" manufacturing process to a bioreactor process and associated change in master cell bank for Aranesp, which entailed a new Phase III study and significant Phase IV post-marketing study follow-up. See Interview with Mark McCamish, Global Head of Biopharmaceutical Dev., Sandoz Int'l, available at http://www.iirusa.com/upload/wysiwyg/2010-P-Div/P1586/Podcast/Podcast_Script_MarkMcCamish.pdf. On the other hand, not all changes that might appear to be significant ex ante prove to have a significant clinical effect; in gaining approval for Avonex, Biogen was able to rely on clinical studies conducted in entirely different cell lines (Biogen produced Avonex in a unique CHO cell line). See Günter Blaich et al., *Overview: Differentiating Issues in the Development of Macromolecules Compared with Small Molecules*, in HANDBOOK OF PHARM. BIOTECHNOLOGY 109–10 (Shane Cox Gad ed., 2007).

²⁵ See Grabowski et al., *supra* note 23, at 1294.

²⁶ See *id.* at 1295–98.

²⁷ *Id.* at 1298–99.

range of strategic responses by manufacturers of innovative biologics and biosimilars will emerge. In this Article, we examine each of these interrelated factors as they affect supply- and demand-side incentives.

II. FDA REGULATIONS AND THE EXPENSE OF DEVELOPING A BIOSIMILAR

The new law authorizing biosimilars gives broad latitude to the FDA to define the process and standards it will apply to biosimilar-marketing approvals.²⁸ FDA decisions will have an impact on both the demand for, and supply, of biosimilars:

- The level of clinical trial and other evidence required to establish either interchangeability or similarity will affect not only regulatory approval but also adoption, as greater levels of evidence will increase physician, payer, and patient confidence in a biosimilar medicine. As a result, the level of evidence required will have an impact on the costs of market entry, number of biosimilar entrants, and assets and capabilities required to compete successfully;²⁹
- Naming conventions and pharmacovigilance requirements for biosimilars will have an impact on entry and perceptions of substitutability by physicians, payers, and patients;³⁰
- Whether data on one indication can be extrapolated to others—absent additional clinical trials in that patient population—safely and without creating a potential for “off-label” liability will have an impact on entry decisions, perceptions of substitutability, and biosimilar uptake;³¹
- Definitions of what will constitute changes in “safety, purity, or potency,” as they are applied to determine whether NBE exclusivity is to be authorized for next-generation

²⁸ 42 U.S.C. § 262(a), (k)(3)–(6), (k)(8) (Supp. IV 2010).

²⁹ See Grabowski et al., *supra* note 23, at 1296–98. This includes whether foreign data will be accepted that use non-U.S.-licensed biologic products as comparators. *Id.*

³⁰ *Id.* at 1298. The FDA notes that patient-safety protection will require distinguishing among the reference product, related biological products that have not been demonstrated to be biosimilar, biosimilar products, and interchangeable products. See U.S. DEP’T OF HEALTH & HUMAN SERVS, FOOD & DRUG ADMIN., DOCKET NO. FDA-2010-N-0477, APPROVAL PATHWAY FOR BIOSIMILAR AND INTERCHANGEABLE BIOLOGICAL PRODUCTS; PUBLIC HEARING; REQUEST FOR COMMENTS 64–101 (2010) [hereinafter FOOD & DRUG ADMIN. HEARING].

³¹ See Grabowski et al., *supra* note 23, at 1296–98.

products will have an impact on biotech-investor incentives.³²

The FDA conducted a two-day public hearing in November 2010 to solicit comments on these and other issues.³³ In addition to the points noted above, the FDA panel also gathered input on the phenomenon of “drift” (i.e., post-market changes to the reference product caused by manufacturing changes) and the effect of the drift on the consideration of interchangeability ratings.³⁴ On the one hand, some expressed concern as to whether the potential for drift calls into question whether products can ever be considered interchangeable, given that drift will result in both the reference product and the biosimilar changing separately over time following biosimilar approval, potentially increasing initial dissimilarities between the drugs.³⁵ On the other hand, some argued that the FDA’s process for assessing the changes in a reference product over time, due to drift, through comparability studies recognizes that a marketed reference product may differ from the version of the reference product used in clinical trials for approval, and supports the idea of weaker standards for interchangeability ratings for biosimilars.³⁶ One proposal for dealing with these challenges is establishing a post-marketing system to monitor interchangeability.³⁷ This system could require strong pharmacovigilance and reporting standards and could potentially allow biosimilars to achieve interchangeability status after the product has been observed on the market for some period of time.³⁸ In particular, the FDA requirements for evidence submitted as part of a biosimilar application will have far-reaching effects on the development of the biosimilar and innovative biotech markets. The law specifies that in reviewing biosimilar applications, the FDA will rely on the results of analytic, animal testing, and clinical-trial data, but it is left to the agency to determine in a particular instance precisely what studies it will require.³⁹ For a given biosimilar application, therefore, the FDA could theoretically require a manufacturer to conduct, at one extreme, only a bioequivalence study (similar to what is required for

³² See 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc), (k)(7)(C)(ii)(II) (Supp. IV 2010).

³³ FOOD & DRUG ADMIN. HEARING, *supra* note 30.

³⁴ *Id.* at 251–70.

³⁵ *Id.*

³⁶ *Id.*

³⁷ *Id.* at 41.

³⁸ See Chad Landmon & Elizabeth Retersdorf, *Challenges of FDA’s Nascent Biosimilar Regime*, LAW360 (Nov. 17, 2010), <http://www.law360.com/web/articles/208593>.

³⁹ BPCIA, Pub. L. No. 111-148, § 7002(k)(2)(A), 124 Stat. 119, 805 (2010).

generic approval under Hatch-Waxman Act⁴⁰) or, at the other extreme, when science and experience do not allow it, a full program of clinical studies equivalent to that included in a biologic licensing application (BLA).⁴¹ For the foreseeable future, the FDA is likely to apply requirements that reflect the relative state of knowledge and complexity of the molecule under review. Current FDA Commissioner Margaret Hamburg signaled this position when she stated, “there will not be a ‘one-size-fits-all’ approach. There will, rather, be a science-driven, case-by-case decision-making process rooted in the regulatory studies that I would encourage your [Generic Pharmaceutical Association] industry to support.”⁴²

Also, the FDA will need to determine what evidence the applicant must submit to achieve a rating of interchangeability with the reference biologic,⁴³ versus a finding of biosimilarity.⁴⁴ Achieving an FDA finding of interchangeability may be associated with far greater development costs than achieving a determination of biosimilarity, or it may be limited initially to a select few examples where molecules meet certain tests for establishing “sameness” through differentiated characterization or other technology being available and validated.⁴⁵ For instance, the FDA’s recent approval of Sandoz’s ANDA for generic enoxaparin sodium (referencing Lovenox), although not a biosimilar (Momenta and Sandoz describe Lovenox, a chemically synthesized product derived from natural sources, as a complex mixture),⁴⁶ may give some insight into the FDA’s current approach, and it may also apply to more complex molecules and to findings of interchangeability.⁴⁷

⁴⁰ Pub. L. No. 98-417, 98 Stat. 1585 (1984).

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

⁴² Margaret A. Hamburg, Comm’r, Food & Drug Admin., Remarks at Generic Pharm. Ass’n Annual Meeting (Feb. 18, 2010), *available at* <http://www.fda.gov/NewsEvents/Speeches/ucm201833.htm>.

⁴³ § 262(k)(4).

⁴⁴ § 262(k)(2)(A)(i)(I).

⁴⁵ *See infra* Part III.A.

⁴⁶ *See, e.g., Generic, MOMENTA*, <http://www.momentapharma.com/pipeline/generic.html> (last visited Mar. 6, 2011).

⁴⁷ *See FDA Approves First Generic Enoxaparin Sodium Injection*, FOOD & DRUG ADMIN. (July 23, 2010), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm>; *see also* Letter from Keith Webber, Deputy Dir., Office of Pharm. Sci., Ctr. for Drug Evaluation and Research, FDA, to Marcy Macdonald, Dir., Regulatory Affairs, Sandoz Int’l (July 23, 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/077857s000ltr.pdf (approving the ANDA). The five criteria the FDA applied in its review are summarized in Part III.

The European Union has had a well-defined regulatory pathway for biosimilars in place for several years which provides one model that could inform how the FDA will elect to proceed.⁴⁸ The European Medicines Agency (EMA) adopted a framework that includes an overarching set of principles;⁴⁹ general guidelines on quality, safety and efficacy;⁵⁰ and product class-specific guidelines.⁵¹ To date, the EMA has issued guidelines in six therapeutic classes⁵² and has approved biosimilars in three major biologic-product classes—erythropoietins (alpha and zeta), somatropin, and granulocyte-colony

⁴⁸ See Eur. Meds. Agency [EMA], *Guideline on Similar Biological Medicinal Products*, EMEA Doc. No. CHMP/437/04 (Oct. 30, 2005), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf.

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Multidisciplinary: Biosimilar*, EUR. MEDS. AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp (last visited Mar. 6, 2011).

⁵² The product-specific biosimilar guidelines include recombinant Erythropoietins, low-molecular-weight heparins, recombinant interferon alpha, Recombinant Granulocyte-Colony Stimulating Factor, Somatropin, and Recombinant Human Insulin. See generally EMA, *Guideline on Clinical and Non-Clinical Development of Similar Biological Medicinal Products Containing Recombinant Erythropoietins (Revision)*, EMEA Doc. No. CHMP/BMWP/301636/2008 (Mar. 18, 2010), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf; EMA, *Guideline on Clinical and Non-Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight Heparins*, EMEA Doc. No. CHMP/BMWP/118264/07 (Mar. 16, 2009) [hereinafter EMA, EMEA/CHMP/BMWP/118264/07], available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003927.pdf; EMA, *Non-clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Interferon Alfa*, EMEA Doc. No. CHMP/BMWP/102046/2006 (Apr. 23, 2009) [hereinafter EMA, EMEA/CHMP/BMWP/102046/2006], available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003930.pdf; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor*, EMEA Doc. No. CHMP/31329/2005 (Feb. 22, 2006), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Somatropin*, EMEA Doc. No. CHMP/94528/2005 (Feb. 22, 2006), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003956.pdf; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin*, EMEA Doc. No. CHMP/32775/05 (Feb. 22, 2006), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf.

stimulating factors (G-CSFs).⁵³ Guidance for three other major types of biologics are under development; the EMA has circulated a draft guideline for monoclonal antibodies⁵⁴ and concept papers for recombinant follicle stimulation hormone and recombinant interferon beta.⁵⁵ Among monoclonal antibodies are significant biologics, some of which, such as Rituxan, face expiry of important patents in the next several years.⁵⁶ The global market for monoclonal antibodies is estimated to have totaled \$36 billion in 2009 and to exceed \$60 billion in 2015.⁵⁷ In anticipation of European and U.S. developments, Teva Pharmaceuticals began clinical trials for its biosimilar to Rituxan, TL011, in both severe rheumatoid arthritis and CD20-positive diffuse b-cell non-Hodgkin's lymphoma.⁵⁸

The EMA has required at least one Phase II or III clinical trial for biosimilars to demonstrate similar safety and efficacy as their reference molecules and has left questions of substitution to the member states.⁵⁹ If the FDA also requires significant clinical-trial evidence, this will mean a much higher investment to obtain approvals for biosimilars as compared to generics. The cost for biosimilar approval will depend on the number and size of the necessary clinical trials,

⁵³ Ben Hirschler, *EU Prepares for Biosimilar Antibody Drugs*, REUTERS (October 1, 2010 1:05 EDT), <http://www.reuters.com/article/2010/10/01/us-medicines-europe-biosimilars-idUSTRE69047620101001>. The EMA issued a draft guideline for interferon alpha and have followed this with a reflection paper (April 2009). See EMA, EMEA/CHMP/BMWP/118264/07, *supra* note 52; EMA, EMEA/CHMP/BMWP/102046/2006, *supra* note 52.

⁵⁴ See generally EMA, *Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (Draft)*, 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 (circulated November 2010 and open for comments through May 2011).

⁵⁵ EMA, *Concept Paper on Similar Biological Medicinal Products Containing Recombinant Follicle Stimulation Hormone*, EMEA Doc. No. CHMP/BMWP/94899/2010 (Mar. 18, 2010); EMA, *Similar Biological Medicinal Products Containing Recombinant Interferon Beta*, EMEA Doc. No. CHMP/BMWP/86572/2010 (Mar. 18, 2010), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089208.pdf.

⁵⁶ See Table 3 for a list of biologics facing expiry of important patents in the next few years. Other clinically and economically significant monoclonal antibodies include Avastin, Remicade, Herceptin, and Lucentis. See DATAMONITOR, PHARMAVITAE: MONOCLONAL ANTIBODIES: 2010, at 1 (2010).

⁵⁷ DATAMONITOR, *supra* note 56, at 22.

⁵⁸ See Naomi Kresge, *Teva Targets Roche's \$5 Billion Rituxan Cancer Drug in Biosimilar Trial*, BLOOMBERG (May 25, 2010), <http://www.bloomberg.com/news/2010-05-25/teva-targets-roche-s-5-billion-rituxan-cancer-drug-in-biosimilar-trial.html>.

⁵⁹ See FALK EHMANN, BIOSIMILARS—REGULATION STRATEGIES AND PATHWAY IN THE EU (AND US) 25 (2010), available at http://www.dvfa.de/files/die_dvfa/kommissionen/life_science/application/pdf/2_Falk_Ehmann_EMEA.pdf.

the number of indications involved, and other specific FDA requirements. The current requirement for a BLA is typically two large-scale Phase III pivotal trials.⁶⁰ If the FDA requires at least one Phase II/III type study comparable to those undertaken by innovators, then the out-of-pocket costs likely will be in the range of \$20 to \$40 million for the studies alone.⁶¹ In addition, the pre-clinical costs associated with biosimilars may actually be higher for biosimilars than for innovative products as they entail modifying the production process in order to achieve a very specific profile that closely approximates the reference product.⁶² Others have estimated that for very complex biologics, biosimilar development costs could total \$100 to \$150 million and take eight or more years to bring a product to market.⁶³ By contrast, the cost of completing bioequivalence studies for generic drugs is estimated to be only \$1 to \$2 million.⁶⁴

There are important differences between the European and U.S. health care systems, however, that suggest biosimilar market development (and share uptake) may differ between the two regions. Among others, the U.S. environment is more litigious than Europe, and so the FDA may decide to proceed more cautiously and require more clinical data than the EMA has in the past. Nevertheless, in the United States, the FDA approved M-Enoxaparin as a fully substitutable generic, which required no clinical evidence.⁶⁵ By contrast, the EMA would require clinical data to approve a biosimilar application for a low molecular weight heparin.⁶⁶ Costs of an FDA submission for U.S. approval could be lower for biosimilars already on the market in

⁶⁰ See Lisa M. Schwartz & Steven Woloshin, *Lost in Transmission—FDA Drug Information that Never Reaches Clinicians*, 361 NEW ENG. J. MED. 1717, 1717 (2009).

⁶¹ T. Oldham, Presentation at the IBC Conference, Brussels, Belgium: Working Out the Profit Potential for Follow-On Biologics (Mar. 1–4 2005); ELMAR SCHÄFER, OPPORTUNITIES FOR FOBs IN EUROPE: A RISK BENEFIT ANALYSIS WITH EPO 16 (2005), available at http://www.biogenerix.com/publications/21_Schaefer.pdf. Schäfer finds an upper bound of \$80 million, but this estimate assumes two large-scale pivotal trials typically required for a new molecular entity. *Id.*

⁶² See Interview with Mark McCamish, *supra* note 24.

⁶³ See Ludwig Burger, *Battle over Biosimilar Drugs is only for the Brave*, REUTERS (July 2, 2010 11:44 AM BST), <http://uk.reuters.com/article/idUKLNE66102R20100702?rpc=401&feedType=RSS&feedName=stocksNews&rpc=401>.

⁶⁴ See David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics* 6 (FTC Working Paper, 2002), available at <http://www.ftc.gov/be/workpapers/industrydynamicsreiffenwp.pdf>. Reiffen and Ward estimate that the cost of applying for an ANDA was approximately \$1.3 million in the early 1990s. *Id.*

⁶⁵ See Letter from Keith Webber, *supra* note 47.

⁶⁶ See *Generic Enoxaparin Questions and Answers*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientandProviders/ucm220037.htm> (last visited Mar. 6, 2011).

Europe if the biosimilar can rely on previously undertaken European clinical trials when compiling an FDA submission. The FDA, however, has not taken a position yet on whether it will accept clinical studies undertaken for approval in other jurisdictions.⁶⁷ The ability to rely on non-U.S. clinical studies for FDA approval of biosimilars may be an important influence on the U.S. costs of biosimilar approval, at least for some products. At a minimum, the FDA may require some level of “bridging” data to justify the relevance of non-U.S. studies for FDA approval, given that the BPCIA specifies that an applicant must demonstrate that its product is biosimilar to a U.S.-approved reference product,⁶⁸ and also given that biologics licensed in different regions may have different characteristics.⁶⁹

The ongoing cost of manufacturing biological entities is also significantly higher than for chemical entities.⁷⁰ Biosimilar manufacturers would either need to construct expensive plants or obtain long-term lease or purchase agreements with third-parties that have an FDA-approved facility if they do not already have excess suitable manufacturing capacity.⁷¹ In any event, the cost of entry for biosimilars is likely to be an order of magnitude higher than for generic drug products and may be closer to two orders of magnitude higher. The high capital costs of entry together with other features discussed below in Part IV will likely restrict the number and types of entrants, at least initially. Further, initial entry is likely to be targeted to the biologics with largest revenues as well as those where scientific and market feasibility have been demonstrated in Europe.

⁶⁷ Currently, the FDA is considering comments from the November 2010 public hearing on “to what extent, if any, should animal or clinical data comparing a proposed biosimilar product with a non-U.S.-licensed comparator product be used to support a demonstration of biosimilarity to a U.S.-licensed reference product.” Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, 75 Fed. Reg. 61,497, 61,499 (Oct. 5, 2010).

⁶⁸ 42 U.S.C. § 262(i)(4) (Supp. IV 2010). Reference product “means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k).” *Id.*; § 262(k)(2)(A)(i)(I).

⁶⁹ The FDA’s inquiry into the use of bridging data, *see supra* note 67, to justify the use of non-U.S. approved reference products may reflect concerns that non-U.S. approved reference products could possess different characteristics than the U.S. approved counterpart.

⁷⁰ *A Brief Primer on Manufacturing Therapeutic Proteins*, BIOTECHNOLOGY INDUS. ORG., <http://www.bio.org/healthcare/pmp/factsheet1.asp> (last visited Mar. 6, 2011).

⁷¹ *Id.*

III. INTERCHANGEABILITY AND DEMAND SIDE ECONOMIC FACTORS

A. *Regulatory Requirements for Interchangeability*

Another key regulatory issue will be the analytical and clinical evidence necessary for the FDA to deem a biosimilar interchangeable with its reference product, thus enabling automatic substitution without physician approval, subject to relevant state laws. For a biosimilar to be interchangeable, an applicant must demonstrate that the product is biosimilar to the U.S. reference product and that it “can be expected to produce the same clinical result as the reference product in any given patient.”⁷² Taken to the extreme, no product could demonstrate the same result in literally every patient, so the FDA’s guidance on how to interpret this requirement will be an important, and likely contentious, factor. For products used more than once by patients (the majority of biologic products), this will require a demonstration that switching between the biosimilar and reference product poses no additional risk of reduced safety or efficacy beyond that posed by the reference product alone.⁷³ This will likely require crossover trial designs in which patients in clinical trials switch between the products over time. It can be difficult to recruit patients for these trials and potentially expensive to perform at a scale necessary to obtain statistical significance. It is also unclear what factors the FDA will consider in evaluating the potential risks related to alternating or switching between the biosimilar(s) and the reference product. Many firms may elect not to make the investments necessary to pursue interchangeability initially, given the current state of uncertainty and scientific knowledge regarding biosimilars. This is in contrast to generics, where an “A” rating by the FDA recognizes the products as therapeutically equivalent and eligible for substitution by pharmacists without physician approval, subject to state substitution laws, thus driving rapid share loss by the branded reference product.⁷⁴

While there have not yet been any approvals under a new biosimilar pathway in the United States, the FDA has approved two more complex molecules that share some characteristics with biologics, enoxaparin sodium and somatropin, by relying in part on a reference product’s safety and efficacy data.⁷⁵ These approvals may shed light

⁷² BPCIA, Pub. L. No. 111-148, § 7002(k)(4)(A)(ii), 124 Stat. 119, 806 (2010).

⁷³ § 7002(a).

⁷⁴ See THOMAS BROWN, HANDBOOK OF INSTITUTIONAL PHARMACY PRACTICE 482 (4th ed. 2006).

⁷⁵ The FDA approved Momenta’s enoxaparin sodium as a generic version of Sanofi-Aventis’s Lovenox through the ANDA pathway, *see supra* note 47, and approved

on how the FDA will review biosimilars and evaluate interchangeability. The recent FDA approval of Sandoz's and Momenta's enoxaparin sodium ANDA and its comments associated with that approval suggest that the FDA will evaluate biosimilarity and interchangeability on a case-by-case basis, dependent on the state of scientific knowledge in each class of medicines.⁷⁶ In the case of relatively less complex and better-characterized biologics, some biosimilar manufacturers may elect to pursue an interchangeability rating.

Enoxaparin is a chemically-synthesized product, derived from naturally-sourced porcine [or pig] heparin.⁷⁷ In summarizing its reasoning in assigning an AP rating⁷⁸ of interchangeability with respect to the reference product Lovenox and Sandoz and Momenta's enoxaparin sodium, the FDA cited five criteria, some of which are unique to enoxaparin and thus would not apply to recombinant DNA biotechnology products:⁷⁹ (1) equivalence of heparin source material and mode of depolymerization, (2) equivalence of physiochemical properties, (3) equivalence of the elements that constitute the enoxaparin molecule (i.e., the disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species), (4) equivalence in biological and biochemical assays, and (5) equivalence of in vivo pharmacodynamic profile.⁸⁰ The first three criteria ensure that the heparin source material, the chemical reaction used in the production process, and the structure of the active ingredient are equivalent to that of the reference product; the fourth and fifth criteria ensure that the biosimilar has the same degree of therapeutic activity as the reference product. Based on these five criteria, the FDA found the products to be interchangeable and did not require any clinical stu-

Novartis's growth hormone Omnitrope through the § 505(b)(2) pathway. See Letter from Robert Meyer, Dir., Office of Drug Evaluation II, Ctr. for Drug Evaluation & Research, to Beth Brannan, Sandoz Int'l (May 30, 2006), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021426s000LTR.pdf (approving the § 505(b)(2) application).

⁷⁶ See *supra* note 75 and accompanying text.

⁷⁷ *Establishing Active Ingredient Sameness for a Generic Enoxaparin Sodium, a Low Molecular Weight Heparin*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220023.htm> (last visited Mar. 7, 2011) [hereinafter FOOD & DRUG ADMIN., *Generic Enoxaparin Sodium*].

⁷⁸ For an explanation on FDA ratings, see *Orange Book Preface*, FDA, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm> (last visited Mar. 7, 2011).

⁷⁹ FOOD & DRUG ADMIN., *Generic Enoxaparin Sodium*, *supra* note 77.

⁸⁰ *Id.*

dies.⁸¹ This is in contrast to the situation in Europe, where the EMA guideline adopts a biosimilar approach to low-molecular-weight heparins, such as Lovenox, and requires clinical studies for approval but does not consider interchangeability with Lovenox.⁸²

Prior to the M-Enoxaparin approval decision, in June 2006, the FDA approved Novartis's growth hormone, Omnitrope, as a follow-on protein to Pfizer's Genotropin.⁸³ Because some older biologics such as human recombinant insulin and growth hormone were approved as new drugs through the New Drug Application (NDA) process under the FD&C Act, the § 505(b)2 pathway under that Act allows the FDA to rely on published scientific literature or its previous findings for similar products as the basis for approval.⁸⁴ The FDA narrowly limited Omnitrope's approval as applying to protein products approved as NDAs, which also had a single active ingredient, a well-understood mechanism of action, and could be well-characterized by existing technology.⁸⁵ While Omnitrope met all these criteria, the FDA did not find sufficient data to rate the product therapeutically equivalent or interchangeable with Genotropin or other approved human growth hormones.⁸⁶

The approval of M-Enoxaparin and Omnitrope may have limited lessons for, and applicability to, the expected FDA requirements for biosimilar approval for more complex biologics with expiring patents in the near future, including the G-CSFs, erythropoietin, and interfe-

⁸¹ *Generic Enoxaparin Questions and Answers*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientandProviders/ucm220037.htm> (last visited Mar. 7, 2011).

⁸² *Id.*

⁸³ See Letter from Robert Meyer, *supra* note 75.

⁸⁴ *Follow-on Protein Products: Hearing Before the H. Comm. on Oversight and Gov't Reform*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Med. Officer, FDA), available at <http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm>.

⁸⁵ *Omnitrope (somatropin [rDNA origin]) Questions and Answers*, FOOD & DRUG ADMIN. (accessed through Wayback Machine), <http://replay.waybackmachine.org/20090513141602/http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm> (last visited Mar. 7, 2011) [hereinafter FOOD & DRUG ADMIN., *Omnitrope Q&A*]; see also Letter from Steven Galson, Dir., Ctr. for Drug Evaluation & Research, FOOD & DRUG ADMIN., to Kathleen Sanzo, Morgan, Lewis & Bockius LLP, Stephan Lawton, Biotechnology Indus. Org., and Stephen Juelsgaard, Genentech 7-8 (May 30, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> (denying various Citizen Petitions that opposed approval of Omnitrope).

⁸⁶ FOOD & DRUG ADMIN., *Omnitrope Q&A*, *supra* note 85.

ron beta.⁸⁷ For the foreseeable future, applications for biosimilars in these classes of more complex biologics are likely to require some clinical-trial data for approval and, even more complicated, costly clinical trials to satisfy the law's requirements to be approved as an interchangeable product. The scope and extent of evidence necessary to demonstrate similarity is likely to evolve over time in accordance with Commissioner Hamburg's statement of a case-by-case regulatory process, which reflects ongoing scientific and technological developments.⁸⁸

B. Patient and Physician Perspectives

The rate of biosimilar penetration is expected to vary by disease indication, patient type, physician specialty, and other factors. As noted, rates of patient and physician acceptance of biosimilars are expected to be lower when the biosimilar lacks an interchangeability rating. In addition, rates of biosimilar acceptance may vary according to such physician and patient-focused factors as: whether the physician specialty is historically more price-sensitive or exhibits greater levels of brand loyalty in therapy choice (e.g., primary care physicians versus specialists, allergists versus rheumatologists); whether the biosimilars will be used over long periods of time as maintenance therapy or only once or twice during a narrow clinical window of treatment opportunity (particularly if long-term clinical data is not available); whether the indication is life-threatening or the implications of therapeutic non-response or adverse reactions are perceived to be very serious; or whether the difference in ease-of-use or out-of-pocket cost to the patient of the brand instead of the biosimilar is expected to be high.⁸⁹

When patients are stable on a given maintenance therapy, biosimilar substitution may tend to be concentrated among new patient starts. As a result, the penetration of biosimilars for indications with a

⁸⁷ As noted earlier, following both the FDA approval of M-Enoxaparin and Omnitrope, the FDA specified that those approvals did not necessarily set precedents for future approvals of other biologic therapies. It is therefore, the authors' opinion that the approvals of M-Enoxaparin and Omnitrope may provide limited guidance on potential FDA requirements for biosimilar approval of more complex biologics where less may be known about the structure of the molecule and the mechanism of action.

⁸⁸ See Hamburg, *supra* note 42.

⁸⁹ See generally Henry Grabowski et al., The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions (Aug. 2007) (unpublished White Paper, Duke Univ. Dep't of Econ.), available at http://econ.duke.edu/Papers/PDF/0907_H_Grabowski_I_Cockburn_G_Long_et_al_Effect_on_Federal_Spending_of_Follow_on_Biologics.pdf.

low rate of turnover in the patient populations may be more limited if products are not interchangeable. The degree of biosimilar uptake will also depend on cost differences and incentives to utilize biosimilars employed by managed care and government payers, as discussed below.⁹⁰ These financial incentives, however, are likely to be tempered if existing patients are responding well to an established therapy. This factor, together with additional factors—specialists' brand loyalty, clinically-vulnerable patient populations, and physician conservatism in switching stable patients to new therapies—are likely to constrain rates of biosimilar uptake for existing patients below levels observed for new patients.⁹¹

Another important demand-side factor is the perspective of specialist physicians and patient groups concerning biosimilars. Physicians who have years of experience with the reference biologic may be reluctant to substitute a biosimilar even for new patients until sufficient experience has accumulated in clinical practice settings, as opposed to clinical trials, provided there is patient access to the reference product.⁹² In order to stimulate demand, it may be necessary for biosimilar firms to establish "reputation bonds" with physicians through strategies similar to those employed by branded firms that communicate information to establish brand value through physician detailing, publications, advertising, and education programs.⁹³ In addition, patient assistance programs and contracts with health plans, pharmacy benefit managers (PBMs), hospitals, or provider groups, which will exercise control over therapy choice, may be used in a targeted way to strengthen the economic proposition associated with biosimilar adoption. These tactics will increase the cost of drug distribution and marketing for biosimilars compared to generics where such marketing and sales costs are minimal and demand is purely driven by lower price and pharmacy contracts for availability.

C. *Reimbursement and Payer Considerations*

Even if biosimilars are viewed as therapeutic alternatives rather than equivalents, hospital or insurer pharmacy and therapeutic (P&T) committees may determine that they are similar enough to institute various incentives to encourage biosimilar utilization, at least for new patients. This cost sensitivity may vary across different payer groups, including private insurers, Medicaid, and Medicare.

⁹⁰ See *infra* Part III.C.

⁹¹ See Grabowski et al., *supra* note 89, at 36.

⁹² See *id.* at 36–37.

⁹³ See *id.* at 36.

1. Private Insurers

Historically, managed care plans have been reluctant to restrict access or pursue aggressive cost-control measures⁹⁴ because many biologic therapies are targeted to cancer and other diseases that are life-threatening or involve serious disability, and have often been without close substitutes. In addition, biologics are often managed within plans as medical benefits rather than pharmacy benefits, and are typically less subject to centralized controls or formulary restrictions.⁹⁵ This has been changing over the last several years, particularly in indications where there is a choice between multiple brand-name biologics. The introduction of biosimilars can be expected to accelerate these trends toward more active management of biologic choice, costs, and utilization.

The relatively high price of biologic treatments, and their growing utilization, indicates that payers have substantial incentives to actively manage access to these therapies and implement access restrictions and incentives that encourage the use of lower-priced biologics and biosimilars. Over the past decade, even with respect to non-interchangeable branded biologics, public and private health insurance plans have begun to develop and put into place medical management, network design, and benefit design strategies to control access to, and utilization of, biologic therapies. Prior authorization or step-edit requirements and formulary tiering with preferred products are used by commercial health insurance plans to manage specialty pharmaceuticals.⁹⁶ The use of specialty tiers—in which patient financial contribution is in the form of coinsurance rather than co-payment—has also been growing and the introduction of lower-priced biosimilars may further accelerate a trend towards multiple specialty tiers and preferred specialty therapies.⁹⁷

⁹⁴ See Grabowski et al., *supra* note 23, at 1295.

⁹⁵ See *id.*

⁹⁶ See Debbie Stern & Debi Reissman, *Specialty Pharmacy Cost Management Strategies of Private Health Care Payers*, 12 J. MANAGED CARE PHARMACY 736, 741 (2006) (citing HEALTH STRATEGY GRP., MCO TRENDS IN SPECIALTY PHARMACY MANAGEMENT (2004)), available at <http://www.amcp.org/data/jmcp/736-744.pdf>. See generally C. Daniel Mullins et al., *Health Plan's Strategies for Managing Outpatient Specialty Pharmaceuticals*, 25 HEALTH AFFS. 1332 (2006).

⁹⁷ See Stern & Reissman, *supra* note 96, at 740–41.

2. Medicare

Medicare reimburses biologics under either the Part B or the Part D program, depending largely on the mode of administration.⁹⁸ Many biologic drugs are currently dispensed in a physician's office, clinic, or hospital as infused agents.⁹⁹ The use of these biologics for Medicare patients is covered under the Medicare Part B program, while self-injectable biologics dispensed in pharmacies (including by specialty pharmacy or mail-order programs) are covered by the Part D program.¹⁰⁰

i. Medicare Part B

In designing the new abbreviated pathway for biosimilars, Congress was concerned that the current Medicare rules for reimbursement of drugs administered under Part B would provide inadequate financial incentives for providers to utilize lower-priced biosimilars.¹⁰¹ Part B drugs are often purchased through a "buy and bill" approach by providers who also make decisions about which therapies are appropriate for a given patient.¹⁰² The provider is reimbursed by Medicare for administering a Part B drug, and the level of reimbursement is based on the weighted average selling price (ASP) for the category to which the drug belongs (the "J-code"), plus six percent.¹⁰³ When generics are assigned to the same J-code as their reference new chemical entity, the physician receives the same level of reimbursement, the volume-weighted average ASP for all manufacturers' products, regardless of whether he or she uses the generic or the reference product.¹⁰⁴ This may provide a strong incentive for physicians to util-

⁹⁸ CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP'T OF HEALTH & HUMAN SERVS., YOUR MEDICARE BENEFITS 21 (2011), available at <http://www.medicare.gov/Publications/Pubs/pdf/10116.pdf>.

⁹⁹ *Id.*

¹⁰⁰ *Medicare Part B (Medical Insurance)*, MEDICARE.GOV, <http://www.medicare.gov/navigation/medicare-basics/medicare-benefits/part-b.aspx> (last visited Mar. 6, 2011); *Medicare Part D (Medicare Prescription Drug Coverage)*, MEDICARE.GOV, <http://www.medicare.gov/navigation/medicare-basics/medicare-benefits/part-d.aspx> (last visited Mar. 6, 2011).

¹⁰¹ See MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: IMPROVING INCENTIVES IN THE MEDICARE PROGRAM 124–29 (2009).

¹⁰² See, e.g., CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP'T OF HEALTH & HUMAN SERVS., COMPETITIVE ACQUISITION PROGRAM (CAP) FOR PART B DRUGS (2005), available at <https://www.cms.gov/transmittals/downloads/R777CP.pdf>.

¹⁰³ BPCIA, Pub. L. No. 111-148, § 3139, 124 Stat. 119, 439 (2010).

¹⁰⁴ MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 118–19; see also CONG. BUDGET OFFICE, PUB. NO. 4043, EFFECTS OF USING GENERIC DRUGS ON MEDICARE'S PRESCRIPTION DRUG SPENDING (2010).

ize the lower-cost generic product, depending on the net-acquisition cost of both products to the physician, reflecting any contracts that may be in place with the brand manufacturer and the pricing strategy of the generic entrant.¹⁰⁵ Biosimilars may not be deemed interchangeable by the FDA, however, and therefore would not be assigned to the same J-code as the brand product.¹⁰⁶ Legislators were concerned that in such instances reimbursement incentives would encourage utilizing the more expensive (higher ASP) reference product for patients, as reimbursement is based on ASP plus six percent.¹⁰⁷

To mitigate potential financial disincentives for physicians to adopt biosimilars, the new legislation sets biosimilar reimbursement under Medicare Part B at the sum of the biosimilar's ASP and six percent of the ASP of the reference biologic product.¹⁰⁸ The reference biologic product will continue to be reimbursed at its own ASP plus six percent.¹⁰⁹ By basing the six percent payment to providers on the reference brand's ASP, the legislation seeks to mitigate provider disincentives to adopt lower cost biosimilars when they are not deemed to be interchangeable and are placed in separate J-codes.¹¹⁰ Whether this reimbursement provision will be sufficient to overcome physician experience and loyalty to the reference biologic, as well as other financial incentives, is an open question. Stronger financial incentives had been proposed by some, including two forms of reference pricing that have had only limited use in the Medicare program, least costly alternative (LCA) requirements and functional equivalents.¹¹¹ A recent case involving Part B inhalation drugs constrained the authority of the Centers for Medicare & Medicaid Services (CMS) and its regional carriers to apply LCA requirements without statutory

¹⁰⁵ MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 107.

¹⁰⁶ *Id.* at 107–08.

¹⁰⁷ *Id.* at 115–16. An individual provider's incentives will depend upon the relative net-acquisition cost of the brand and biosimilar versions of the product. Brand manufacturers selectively lower the acquisition costs for providers through contracting, depending upon volume or other criteria, which in turn affects ASP. *Id.* at 130 n.13.

¹⁰⁸ BPCIA § 3139.

¹⁰⁹ *Id.*

¹¹⁰ Others have raised concerns over shared J-codes due to “track and trace” public health requirements. *See, e.g.*, The Deficit Reduction Act of 2005, Pub. L. No 109-171, § 6002, 120 Stat. 4, 59 (2005) (requiring physicians to include the National Drug Code (NDC) in addition to the J-code on Medicaid reimbursement forms). Without the NDC code, Medicaid is unable to identify the corresponding manufacturer on shared J-code claims and therefore, is unable to request Medicaid rebates from the manufacturer.

¹¹¹ MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 124–29.

changes, concluding that the statutory direction to CMS reimbursement using ASP precluded its using LCA policies.¹¹² A functional equivalent approach had been used by CMS in its 2003 hospital outpatient payment rule, reimbursing both darbepoetin alfa and epoetin alfa at the same rate, based on a finding that “the two products are functionally equivalent” and “produce the same clinical result.”¹¹³ Later, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) limited the application of the functional equivalent standard and prohibited its use for other drugs and biologics in determining hospital outpatient payments.¹¹⁴ While biosimilar reimbursement methodology is specified under the new statute, coverage decisions by regional carriers may vary and also could prove to be important, as suggested by the LCA example.

ii. Medicare Part D

Privately offered Medicare Part D drug programs cover retail drugs including self-injectable biologics.¹¹⁵ Biologics accounted for only six percent of total prescription drug costs in the Medicare Part D program in 2007;¹¹⁶ however, spending for biologics within the Part D program is expected to increase rapidly over the coming years. Between 2006 and 2007, biologic prescription drug costs within the Part D program grew by thirty-six percent, exceeding the overall Part D expenditure growth of twenty-two percent.¹¹⁷ Expenditures for self-injected biologics are expected to continue to grow rapidly in the future, as they are increasingly used to treat a wide range of diseases, such as rheumatoid arthritis, and given the large number of new biologics currently under development. The high price of self-injected biologics relative to traditional new chemical entities (NCEs) also suggests that biologics will comprise an increasing share of Part D expenditures in the future. This may lead payers to pursue pharmacy

¹¹² See, e.g., *Hays v. Sebelius*, 589 F.3d 1279, 1282 (D.C. Cir. 2009).

¹¹³ Changes to the Hospital Outpatient PPS and Calendar Year 2003 Payment Rates, 67 Fed. Reg. 66,718, 66,758, (Nov. 1, 2002) (to be codified at CFR 42 pts. 405, 419).

¹¹⁴ See Patricia Seliger Keenan et al., *Biotechnology and Medicare's New Technology Policy: Lessons from Three Case Studies*, 25 HEALTH AFFS. 1260, 1262 (2006), available at <http://content.healthaffairs.org/cgi/reprint/25/5/1260>.

¹¹⁵ MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 120; *Medicare Part D (Medicare Prescription Drug Coverage)*, *supra* note 100.

¹¹⁶ JOAN SOKOLOVSKY & HANNAH MILLER, MEDICARE PAYMENT ADVISORY COMM'N, MEDICARE PAYMENT SYSTEMS AND FOLLOW-ON BIOLOGICS 8 (2009), available at <http://www.medpac.gov/transcripts/followon%20biologics.pdf>.

¹¹⁷ *Id.*

management techniques aimed at controlling utilization of these biologics.¹¹⁸

Many Medicare Part D plan designs include a specialty-drug tier, with average coinsurance rates increasing from twenty-five percent in 2006 to thirty-three percent in 2009.¹¹⁹ Coinsurance plan designs could produce strong incentives to utilize biosimilars if substantial discounts emerge for biologic products with expensive courses of treatment for patients.¹²⁰ Preferred specialty drugs might be subject to lower rates of coinsurance, to a copayment rather than to coinsurance, or to lower patient out-of-pocket costs at the same coinsurance rate.

One limiting factor to formulary incentives for biologics in Medicare Part D is that enrollees with low-income subsidies make up a disproportionately large share of the market for biologics under the Part D program.¹²¹ Given that these individuals are subject to limited cost sharing, other instruments such as step therapy and prior authorization may be employed to incentivize the use of biosimilars.¹²²

Finally, there is uncertainty as to whether biosimilars will be treated as brands or generics for purposes of mandated manufacturer pricing, and therefore patient costs, during the transition period under the federal health care reform law to eliminate the coverage gap or “donut hole” in the Part D program.¹²³ Starting in 2011, brand products are required to be sold at a 50% price discount to enrollees when their spending is in the coverage gap.¹²⁴ Generic products are subject to no such requirement.¹²⁵ Plan cost-sharing requirements over the 2011 to 2020 period also differ between brand and generic products. It is currently unclear how CMS will treat biosimilars with respect to spending in the coverage gap, and whether they will face the same price discount and cost-sharing requirements as branded

¹¹⁸ See Grabowski et al., *supra* note 23, at 1294–95.

¹¹⁹ 2009 plan designs were applied to 2008 plan enrollments for calculations. See ELIZABETH HARGRAVE ET AL., KAISER FAMILY FOUND., MEDICARE PART D 2008 DATA SPOTLIGHT: SPECIALTY TIERS (2007), available at <http://www.kff.org/medicare/upload/7711.pdf>; JACK HOADLEY ET AL., MEDICARE PAYMENT ADVISORY COMM’N, MEDICARE PART D BENEFIT DESIGNS AND FORMULARIES, 2006–2009 (2008), available at <http://www.medpac.gov/transcripts/MedPAC%20Formulary%20Presentation%20-%20Hoadley%2012-05-08%20revised.pdf>.

¹²⁰ HARGRAVE ET AL., *supra* note 119.

¹²¹ CONG. BUDGET OFFICE, *supra* note 104, at 4 fig.1 (2010).

¹²² *Id.* at 6.

¹²³ *Id.* at 21.

¹²⁴ *Id.* at 3.

¹²⁵ *Id.*; see *id.* at tbl.1.

drugs, or if they will be treated similarly to generics in this respect and face no price discount requirements.¹²⁶ If CMS were to categorize biosimilar drugs with generics for this purpose, there could be circumstances during the transition years in which it is economically attractive for patients and plans to utilize the reference brand over biosimilars, taking into account the “donut hole” discounts by brands relative to biosimilar discounts, the cost-sharing requirements for brands and generics, and related economic factors.¹²⁷ CMS has not announced how biosimilars will be categorized for the purpose of the Part D “donut hole” discounting requirement.

3. Medicaid

Medicaid Preferred Drug Lists (PDLs) reflect preferred biologic products in a number of therapeutic categories. Preferred drugs typically can be dispensed without undergoing access controls such as prior authorization which are applied to non-preferred drugs. For example, on-line PDLs for Florida, Illinois, New York, Ohio, Pennsylvania and Texas, indicate that current rheumatoid arthritis (RA), hepatitis C (HCV), and human growth hormone formularies in these six large states preferred two or three RA agents (of six), one or two HCV agents (of five), and between two and five human growth hormones (of nine agents/forms).¹²⁸ Medicaid programs can be expected to encourage biosimilars through PDLs and other medical management instruments. States with managed Medicaid programs apply formulary and access management techniques common in commercial insurance plans.¹²⁹

¹²⁶ *Id.* at 20–21.

¹²⁷ CONG. BUDGET OFFICE, *supra* note 104, at 20–21.

¹²⁸ See FLA. AGENCY FOR HEALTH CARE ADMIN., FLORIDA MEDICAID PREFERRED DRUG LIST (2011), *available at* http://ahca.myflorida.com/Medicaid/Prescribed_Drug/pharm_thera/pdf/pdl.pdf; ILL. MEDICAID, PREFERRED DRUG LIST (2011), *available at* <http://www.hfs.illinois.gov/assets/pdl.pdf>; OHIO MEDICAID, PREFERRED DRUG LIST (2010), *available at* <http://jfs.ohio.gov/ohp/bhpp/PDLQuicklist.pdf>; PA. MEDICAID, MEDICAL ASSISTANCE FEE-FOR-SERVICE PREFERRED DRUG LIST (2010), *available at* http://www.providersynergies.com/services/documents/PAM_PDL_20110215.pdf; TEX. HEALTH & HUMAN SERVS., TEXAS MEDICAID PREFERRED DRUG LIST (2011), *available at* http://www.txvendordrug.com/downloads/pdl/TXPDL_012011.pdf; NYS Medicaid Pharmacy Prior Authorization Programs, MAGELLAN MEDICAID ADMIN., https://newyork.fhsc.com/enrollees/PDP_about.asp (last visited Mar. 6, 2011).

¹²⁹ ROBERT NAVARRO, *MANAGED CARE PHARMACY PRACTICE* 77 (2d ed. 2009).

4. Hospitals

Hospitals typically bear the costs of biologics used during inpatient hospital stays as part of a fixed global reimbursement payment scheme that includes other services and products. Consequently, these hospitals have incentives to implement access restrictions and other mechanisms that encourage the use of lower-priced biologics and biosimilars.¹³⁰ As a result, for biologics that are generally used in hospital settings, hospitals will play a larger role than insurance companies in affecting the demand for biosimilar therapies. In the hospital sector, P&T committees review the drugs that are stocked, on standing order forms, and which can be used by physicians. Hospitals also rely on Group Purchasing Organizations (GPOs) to gain leverage in negotiating discounts from suppliers, including biologic manufacturers.¹³¹ Because the hospital GPO market is highly concentrated, favorable contracts with a handful of suppliers can have an important effect on product selection. In addition, fixed diagnosis-related group-based reimbursement creates strong incentives for input-cost reductions where possible.¹³² To the degree that biologics used in the inpatient hospital setting are included in diagnosis-related groups (DRGs), depending on how significant a portion of spending they represent, hospitals may be aggressive in implementing financial incentives and access controls to favor the utilization of some biosimilars if biosimilar prices are not countered by the brand name manufacturers.

¹³⁰ See, e.g., CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP'T OF HEALTH & HUMAN SERVS., MEDICARE CLAIMS PROCESSING MANUAL, CHAPTER 17: DRUGS AND BIOLOGICS (2010) (outlining the incentive structure for biologics), available at <https://www.cms.gov/manuals/downloads/clm104c17.pdf>.

¹³¹ See, e.g., OFFICE OF THE INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUMAN SERVS., REVIEW OF REVENUE FROM VENDORS AT THREE GROUP PURCHASING ORGANIZATIONS AND THEIR MEMBERS (2005), available at <http://oig.hhs.gov/oas/reports/region5/50300074.pdf>.

¹³² DRGs are used to classify the type of treatment that a patient receives while admitted at a hospital for inpatient care. The specific DRG assigned to a case is determined based on diagnoses, procedures, discharge status, and patient characteristics for that episode of care. For most cases, Medicare reimburses hospitals a fixed amount for an inpatient episode of care based on the assigned DRG irrespective of the actual costs incurred by the hospital for that specific patient. See e.g., U.S. DEP'T OF HEALTH & HUMAN SERVS., ACUTE CARE HOSPITAL INPATIENT PROSPECTIVE PAYMENT SYSTEM (2010) (fact sheet regarding Medicare payments to facilities providing acute hospital inpatient care), available at <http://www.cms.gov/MLNProducts/downloads/AcutePaymtSysfctstht.pdf>.

5. Health Care Reform Initiatives

More widespread adoption of comparative- and cost-effectiveness analyses across the U.S. health care system could further influence adoption of biologics in the future. Formal cost-effectiveness reviews by payers have been well-established in geographies outside the United States in the form of Health Technology Assessments (HTAs).¹³³ In the United Kingdom, for example, the National Institute of Health and Clinical Excellence's (NICE) coverage recommendations have been based on strict reviews of cost-effectiveness calculations relative to an implied standard of an acceptable cost per quality-adjusted life year (QALY).¹³⁴ The creation of the new Patient-Centered Outcomes Research Institute (PCORI) as part of the recently enacted U.S. health reform legislation may contribute to further increases in cost- and comparative-effectiveness pressures.¹³⁵

Finally, longer-term changes in reimbursement policies may further shift financial incentives toward the use of biosimilars. For example, the adoption of global-payment strategies, rather than fee-for-service reimbursement, or some form of shared savings, could strengthen the link between physician and/or hospital compensation and use of lower-priced biologics. Global payment strategies provide incentives for the adoption of lower-cost treatments (and potentially encourage greater price competition) by setting a fixed-payment level for a patient/episode of care, with all, or a portion of, cost savings accruing to the care providers.¹³⁶ Several states are considering implementing global-payment strategies, and it has been suggested that government programs such as Medicaid could be the first to implement these strategies.¹³⁷

¹³³ See, e.g., *Measuring Effectiveness and Cost Effectiveness: The QALY*, NAT'L INST. OF HEALTH & CLINICAL EXCELLENCE (Apr. 20, 2010), <http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenesstheqaly.jsp>.

¹³⁴ See *id.*

¹³⁵ BPCIA, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804 (2010) (codified at 42 U.S.C. § 262 (Supp. IV 2010)).

¹³⁶ See HOSPITAL ACUTE INPATIENT SERVICES PAYMENT SYSTEM, MEDPAC 1 (2010), available at http://www.medpac.gov/documents/MedPAC_Payment_Basics_10_hospital.pdf.

¹³⁷ See, e.g., Liz Kowalczyk, *Massachusetts Recasting Health Payments: Officials Draft Plans for New System to Compensate Doctors, Hospitals*, BOSTON GLOBE, Sept. 27, 2010, at Metro 1.

IV. BIOSIMILAR COMPETITION VERSUS GENERIC COMPETITION

A. *Generic Competition*

Since the passage of the Hatch-Waxman Act twenty-five years ago, generic competition has become the main instrument of price competition in the U.S. pharmaceutical market.¹³⁸ Generic products in 2009 accounted for three-quarters of all U.S. prescriptions,¹³⁹ compared to only nineteen percent in 1984.¹⁴⁰ The growth of generic utilization has been accelerated by various formulary and utilization management techniques such as tiered formularies, prior authorization and step edits, higher reimbursements to pharmacies for dispensing generics, and maximum allowable cost (MAC) programs.¹⁴¹

A distinctive pattern of generic competition has been observed in various economic studies.¹⁴² There is a strong positive relationship both between a product's market sales and the likelihood of a patent challenge, and between the number of generic entrants and the intensity of generic price competition once the exclusivity period has expired.¹⁴³ An increasing number of products are now subject to patent challenges earlier in their product life cycle, as generic firms seek out the 180-day exclusivity period awarded to the first firm to file an ANDA with a successful Paragraph IV challenge.¹⁴⁴ Significant products typically experience multiple entrants within the first several months after patent expiration, and generic price levels drop toward marginal costs rapidly as generic entry increases.¹⁴⁵

¹³⁸ See Henry Grabowski et al., *Entry and Competition in Generic Biologics*, 28 *MANAGERIAL & DECISION ECON.* 439, 447 (2007).

¹³⁹ Gary Gatyas, *IMS Health Reports U.S. Prescription Sales Grew 5.1 Percent in 2009, to \$300.3 Billion*, IMS HEALTH (Apr. 1, 2010), <http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=d690a27e9d5b7210VgnVCM100000ed152ca2RCRD>.

¹⁴⁰ FED. TRADE COMM'N, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY I* (2002).

¹⁴¹ See generally Murray Aitken et al., *Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point* 28 *HEALTH AFFS.* w151 (2009) (discussing recent trends in drug spending and the importance of biosimilars in the market).

¹⁴² Henry Grabowski, *Competition Between Generic and Branded Drugs, in PHARMACEUTICAL INNOVATION: INCENTIVES, COMPETITION, AND COST-BENEFIT ANALYSIS IN INTERNATIONAL PERSPECTIVE* 153, 153–73 (Frank A. Sloan & Chee-Ruye Hsieh eds., 2007).

¹⁴³ *Id.* at 158.

¹⁴⁴ *Id.*

¹⁴⁵ *Id.* at 158, 161.

B. Theoretical Models of Biosimilar Competition

Given the much higher costs of entry for biosimilars compared to generic drugs, as well as the other demand- and supply-side factors discussed above, the pattern of biosimilar competition is expected to differ from current generic competition.¹⁴⁶ In particular, fewer entrants and less intensive price discounting are expected and competition may resemble branded competition more than generic competition. This is currently the case in the human growth hormone market, where there are eight products that compete both through price and product delivery differentiation, such as more convenient pen dispensers.¹⁴⁷ In 2006, Sandoz entered the market with Omnitrope but has struggled to gain market share. Initially, Omnitrope was priced at a thirty-percent discount based on wholesale acquisition cost (WAC) compared to the most widely used biologic in this class, Genetropin.¹⁴⁸ By 2008, Omnitrope's discount had increased to forty percent.¹⁴⁹ Despite these discounts, Omnitrope's share of somatotropin use remained below two percent.¹⁵⁰ These outcomes may not be reflective of the substitution potential for biosimilars generally, given that the human growth hormone market is a mature one with a number of competitors, in which an important factor in a product's success is its delivery system.¹⁵¹ Many of the established brands have invested in more sophisticated pen- or needle-free delivery systems compared to the delivery systems used by recent lower-priced entrants.

To date, some theoretical analyses have attempted to model the likely scenarios for biosimilar competition in the U.S. market. Henry Grabowski, David Ridley, and Kevin Schulman focus on how the higher costs of biosimilar entry will influence the number of entrants and the expected discounts.¹⁵² Using a simulation approach, they project a relatively small number of entrants even for larger-selling biologic products, and more modest discounts on biosimilars, than in the case of generics. Devin Chauhan, Adrian Towse, and Jorge Me-

¹⁴⁶ See Grabowski et al., *supra* note 23, at 1292–1300.

¹⁴⁷ See Grabowski et al., *supra* note 89, at 45.

¹⁴⁸ Paul Heldman, Potomac Research Grp., Presentation to the Federal Trade Commission: Follow-on Biologic Market: Initial Lessons and Challenges Ahead (Nov. 21, 2008), *available at* <http://www.ftc.gov/bc/workshops/hcbio/docs/fob/pheldman.pdf>.

¹⁴⁹ See Grabowski et al., *supra* note 89, at 45.

¹⁵⁰ See Heldman, *supra* note 148.

¹⁵¹ See generally Grabowski et al., *supra* note 89.

¹⁵² See generally Grabowski et al., *supra* note 138.

stre-Ferrandiz propose a segmented model of biosimilar competition, in which they expect biosimilars to be utilized significantly in the price-sensitive portion of the market but less so in the non-price-sensitive portion of the market (given the reluctance of many providers to utilize biosimilars until considerable clinical experience has accumulated).¹⁵³ Average price discounts will depend on the relative size of these market segments. The authors expect that, given a relatively small number of branded biosimilar competitors, the innovator will discount prices from pre-entry levels but not to the same level as the biosimilar entrants. This is in contrast to generic competition where branded firms typically do not lower prices post-entry but may license an authorized generic when only a small number of generic competitors are expected as a result of a successful paragraph IV entry with a 180-day exclusivity award.¹⁵⁴

C. *Empirical Studies of Generic Drug Analogues*

Other researchers have attempted to predict how biosimilar competition will emerge by considering analogous situations, including the U.S. generic market for certain products which share some characteristics suggestive of biologics. Grabowski et al. divided small molecule drugs into two classes, non-complex and complex, with complex drugs being those that meet two of the following criteria: black box warnings, narrow therapeutic index, prescribed by specialists, oncology products, or manufacturing technology that is available to only a limited number of firms.¹⁵⁵

They analyzed price and quantity data from IMS Health Inc. for thirty-five conventional (i.e., non-biologic) drugs that experienced generic entry between 1997 and 2003 and found that complex drugs are associated with lower levels of generic share and price discounts.¹⁵⁶ Figure 1 compares the average generic share over time for drugs with two or more of the above complex characteristics to drugs with one or none of these characteristics.¹⁵⁷ One year after initial generic entry, the mean generic share for drugs with two or more complex characteristics was forty-five percent, while drugs with one or no

¹⁵³ DEVEN CHAUHAN ET AL., THE MARKET FOR BIOSIMILARS: EVOLUTION AND POLICY OPTIONS, 45 OFFICE OF HEALTH & ECON. BRIEFING 12–14 (2008).

¹⁵⁴ Ernst R. Berndt et al., *Authorized Generic Drugs, Price Competition, and Consumers' Welfare*, 26 HEALTH AFFS. 790, 792–97 (2007).

¹⁵⁵ See Grabowski et al., *supra* note 89, at 42.

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*

complex characteristics had a mean generic share of seventy-eight percent (1.7 times higher).¹⁵⁸

FIGURE 1¹⁵⁹
Average Generic Share of the Molecule by Complex Drug Characteristics

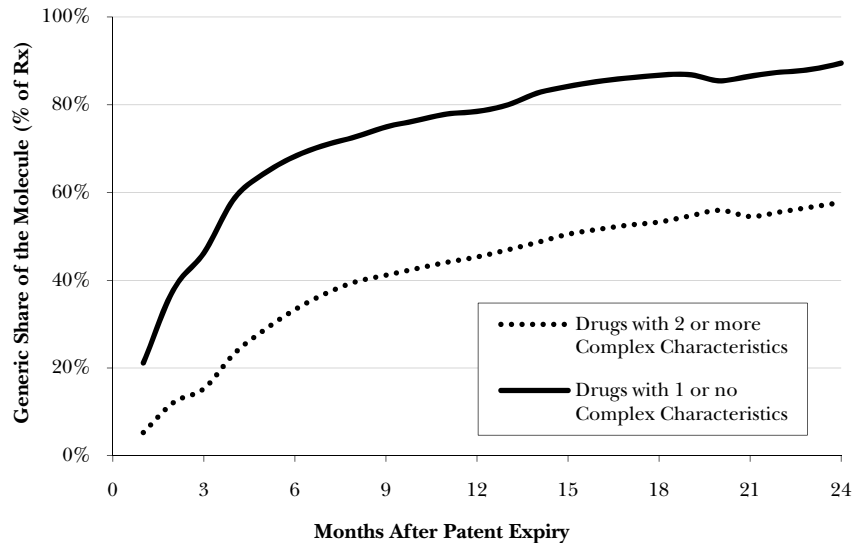


Figure 2 compares the generic price discounts from the brand over time for drugs with two or more of the above complex characteristics to drugs with one or none of these characteristics.¹⁶⁰ One year after initial generic entry, the generic price discount for drugs with two or more complex characteristics was thirty-five percent, while drugs with one or no complex characteristics had a generic discount of fifty-eight percent (1.6 times higher). The lower mean levels of generic shares and price discounts for drugs with two or more complex characteristics are also reflected in a lower number of generic entrants. On average, drugs with two or more characteristics faced 2.5 generic entrants one year following initial generic entry, while

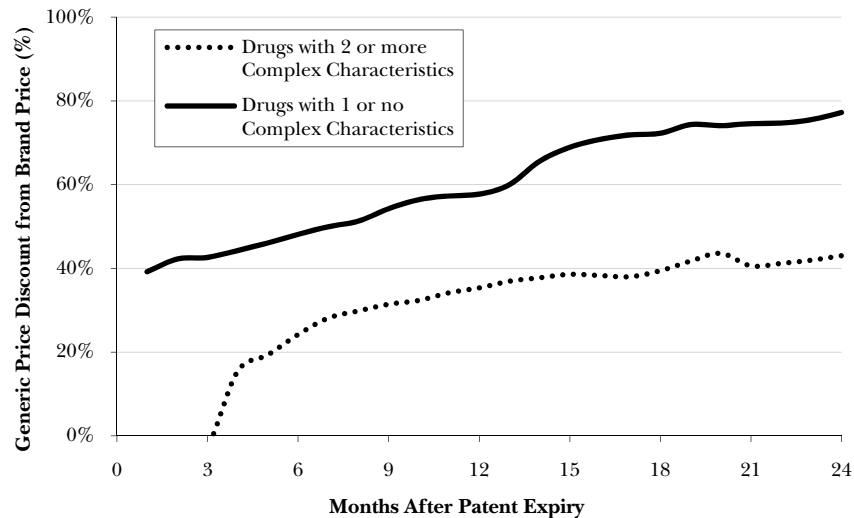
¹⁵⁸ *Id.* at 42–43.

¹⁵⁹ Figure 1 represents the authors' calculations from a sample of 35 drugs experiencing generic entry between 1997 and 2003. The pharmaceutical sales data come from IMS National Sales Perspectives Data. A description of the data source is available at, IMS HEALTH, <http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnnextoid=1cb0eec5accb2210VgnVCM100000ed152ca2RCRD&cpsextcurrchannel=1> (last visited Apr. 12, 2011). The determination of complex characteristics for each drug is based on the authors' research.

¹⁶⁰ *Id.* at 43, 53 fig.2.

drugs with one or no characteristics faced an average of 8.5 generic entrants.

FIGURE 2¹⁶¹
Average Generic Price Discount from Brand Price for the Molecule
by Complex Drug Characteristics



While the data from conventional generics should not be directly applied to estimate biosimilar shares following market entry in the biologics market, they suggest that biosimilar uptake will be significantly lower than is observed today in the case of generic drugs.¹⁶² Even these more complex generic drugs are nevertheless rated therapeutically equivalent (i.e., have an FDA rating of A) and, therefore, benefit from some automatic substitution.¹⁶³ In order to avoid substitution, physicians need to specify in “do not substitute” orders that prescriptions are to be dispensed as written.¹⁶⁴ At least initially, most biosimilars will not likely be rated therapeutically equivalent and,

¹⁶¹ Figure 2 represents the authors’ calculations from a sample of 35 drugs experiencing generic entry between 1997 and 2003. The pharmaceutical sales data come from IMS National Sales Perspectives Data. A description of the data source is available at, IMS HEALTH, <http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnnextoid=1cb0eec5accb2210VgnVCM100000ed152ca2RCRD&cpsexcurrchannel=1> (last visited Apr. 12, 2011). The determination of complex characteristics for each drug is based on the authors’ research.

¹⁶² *Id.* at 43.

¹⁶³ *Id.*

¹⁶⁴ See Grabowski et al., *supra* note 89, at 43.

therefore, will not be subject to automatic substitution.¹⁶⁵ The recent FDA approval of generic enoxaparin, rated as therapeutically equivalent to branded Lovenox (which has an AP rating), will provide important data about competitive pricing strategy and market acceptance of a complex, “biologic-like” product in which only a few competitors are anticipated, based on the technical similarity and manufacturing requirements involved.¹⁶⁶ Currently, the FDA has approved only a single manufacturer’s ANDA,¹⁶⁷ Momenta’s generic enoxaparin, and sales of generic enoxaparin are robust.¹⁶⁸

Table 1 summarizes other market share and price discount analyses generally based on selective aspects of the U.S. generic market. Most notably, as part of the evaluation of the proposed legislation regarding biosimilars, the Congressional Budget Office (CBO) predicted penetration ratios consistent with the analyses of complex drugs in Figures 1 and 2, but expected a longer phase-in period for biosimilar drugs.¹⁶⁹ By year four after market launch, the CBO expects a penetration rate of 35% with price discounts by biosimilars of 40%.¹⁷⁰ Other estimates on market penetration from a pharmacy benefit management firm, Express Scripts, as well as by Avalere Health, a consulting firm, tend to be somewhat higher than either the Grabowski et al. or CBO values, with penetration in the 50% to 60% range, and somewhat higher discounts in the case of the Avalere study (50% by year three).¹⁷¹

¹⁶⁵ *Id.*

¹⁶⁶ See *Generic Enoxaparin Questions and Answers*, *supra* note 81.

¹⁶⁷ The FDA has also reviewed Teva’s ANDA for generic enoxaparin and responded with a “Minor Deficiency” letter. Press Release, Teva, Teva Receives FDA Action Letter for Generic Lovenox (Jan. 25, 2011), available at http://www.tevapharm.com/pr/2011/pr_988.asp. Teva states that prior to final approval of its ANDA it needs to respond to a short list of questions contained on the Minor Deficiency letter and that it plans to submit a response to the FDA in the near future. *Id.*

¹⁶⁸ According to analysts, Momenta’s generic enoxaparin generated \$292 million in sales in its first sixty-nine days on the market. See *Generic Lovenox Feud Back in Spotlight*, RTT NEWS (Oct. 26, 2010), <http://www.rttnews.com/content/topstories.aspx?Id=1457134&pageNum=1>.

¹⁶⁹ See Cong. Budget Office, S. 1695 Biologics Price Competition and Innovation Act of 2007, at 7 (2008).

¹⁷⁰ *Id.*

¹⁷¹ See *infra* tbl.1.

TABLE 1
Biosimilar Competition U.S. Market Share and Price Discount Evidence

Source	Peak Biosimilar Penetration	Biosimilar Discount to Pre-Entry Brand Price	Basis
Grabowski (2007) ¹⁷²	10% – 45%	10%–30% (year 1)	Higher estimates correspond to complex small molecules
CBO (2008) ¹⁷³	10% (year 1) 35% (year 4)	20% (year 1) 40% (year 4)	Similar market situations
Express Scripts (2007) ¹⁷⁴	49%	25% (year 1)	Therapeutic alternatives
Avalere Health (2007) ¹⁷⁵	60%	20% (year 1) 51% (year 3)	Average small molecule generic drug penetration rates

D. Empirical Evidence from Biosimilars in the European Union

Germany has exhibited the highest level of aggregate demand for biosimilar products thus far.¹⁷⁶ Experience in other European countries has been less strong. While evidence from experiences in Germany or other European countries with biosimilar substitution are not directly applicable to the U.S. market, given differences in the markets and reimbursement systems, they nevertheless suggest that over time significant biosimilar share is possible and payers, physicians, and patients will accept biosimilars.¹⁷⁷ In Germany, the biosimilar erythropoietin's sales accounted for nearly 60% of total biosimilar

¹⁷² See Grabowski et al., *supra* note 89, at 9.

¹⁷³ See CONG. BUDGET OFFICE, *supra* note 169, at 7.

¹⁷⁴ See STEVE MILLER & JONAH HOUTS, POTENTIAL SAVINGS OF BIOGENERIC IN THE UNITED STATES 2 (2007), available at <http://www.express-scripts.com/research/studies/pharmacybenefitresearch/specialtypharmacyservices/docs/potentialSavingsBiogeneticsUS.pdf>.

¹⁷⁵ See RONALD KING, AVALERE HEALTH, MODELING FEDERAL COST SAVINGS FROM FOLLOW-ON BIOLOGICS (2007), available at http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf. Biosimilar penetration estimates are for the largest selling products. Avalere Health is conducting further analysis.

¹⁷⁶ See Melanie Senior, *European Biosimilars' Market Performance Mirrors US Legislative Progress: Slow but Steady*, BIOPHARMA TODAY (May 19, 2009), <http://www.biopharmatoday.com/2009/05/european-biosimilars-market-performance-mirrors-us-legislative-progress-slow-but-steady.html>.

¹⁷⁷ TED BUCKLEY, BIOSIMILARS: THE POTENTIAL FOR THE U.S. MARKET 9–15 (2010).

and reference product sales within two years of biosimilar launch; biosimilar G-CSF's accounted for almost 30% of combined biosimilar reference product sales.¹⁷⁸ These biosimilars have been far less successful in France, however, where the biosimilar erythropoietin has less than a 10% share and the biosimilar G-CSF has slightly less than a 20% share.¹⁷⁹ Table 2 summarizes the biosimilar share experiences in Germany and France. Germany's diverse payer environment (where there are hundreds of individual sickness funds) and relatively heavy reliance on generic drugs may suggest greater parallels with the United States. Future research comparing biosimilar market attitudes and experience in various European countries, the United States, and the BRIC countries (Brazil, Russia, India, and China) is needed.

TABLE 2
*Biosimilar Competition Germany and France Market Share Evidence*¹⁸⁰

Biosimilar Shares	Share of Class		Share of Reference Product	
	Germany	France	Germany	France
Erythropoietin				
Q4/07	3.0%	–	8.1%	–
Q1/09	27.2%	0.3%	55.1%	1.5%
Q4/09	28.2%	1.4%	58.3%	6.4%
G-CSFs				
Q4/08	1.5%	–	1.8%	–
Q2/09	23.4%	3.6%	28.1%	4.9%
Q4/09	23.5%	13.0%	27.8%	17.8%

V. PROJECTED SAVINGS TO CONSUMERS

The Congressional Budget Office estimated that the provisions in the current health care law establishing a biosimilar pathway will reduce federal budget deficits by \$7 billion over the 2010 to 2019 pe-

¹⁷⁸ *Id.* at 11–12; see also FED. TRADE COMM'N, HOSPIRA RESPONSES TO FTC QUESTIONS ON BIOSIMILARS (May 19, 2009), available at <http://www.ftc.gov/os/comments/healthcarecompissues/090519hospirasupplementonbiosimilars.pdf> (indicating that one year following the launch of biosimilar EPO in Germany, the biosimilar had almost a fifty-percent share of the EPO market and the biosimilar was priced at a thirty-seven percent discount compared to the average brand price prior to biosimilar entry).

¹⁷⁹ BUCKLEY, *supra* note 177, at 12–13.

¹⁸⁰ See *id.* at 11–13.

riod.¹⁸¹ This finding is consistent with a 2008 CBO study of a similar Senate bill,¹⁸² where it estimated a reduction in federal budget deficits of \$6.6 billion and a reduction in biologic drug spending of \$25 billion for the 2009 to 2018 period.¹⁸³ Over the full ten-year period, the \$25 billion in reduced biologic drug spending would account for roughly 0.5% of national spending on prescription drugs, valued at wholesale prices.¹⁸⁴ The bulk of these estimated savings accrue in the last five years of the ten-year time ranges analyzed. Savings beyond the ten-year period may increase substantially as more biologics lose patent and NBE-exclusivity protections, and as scientific advances are made that both improve the ability to produce biosimilar versions of innovative drugs and reduce the cost of developing biosimilars.¹⁸⁵

Over the next six years, a number of the largest selling biologic products may face losses of some key patent and/or NBE-exclusivity protections. Determining the effective patent expiry date for any given biologic is subject to interpretation, and opinions surely will differ considerably for some patents and products. A number of significant unknowns affect the precision of any such analysis, including the identification of all the patents in the portfolio protecting an individual biologic, the strength of those patents in the face of challenges, and the ability of biosimilar manufacturers to work around existing patents.¹⁸⁶ Based on a review of patent expiry information reported in manufacturers' financial reports and supplemented with additional public information from academic literature, research reports, patent filings, and court documents, the earliest publicly reported potential

¹⁸¹ Letter from Douglas W. Elmendorf, Cong. Budget Office, to the Honorable Nancy Pelosi, Speaker, U.S. House of Representatives (Mar. 20, 2010), available at <http://www.cbo.gov/ftpdocs/113xx/doc11379/AmendReconProp.pdf>.

¹⁸² Both the current health care law and the earlier Senate bill (S. 1695) allow for a twelve-year exclusivity period for the innovator biologic. See CONG. BUDGET OFFICE, *supra* note 169, at 4; see also 42 U.S.C. § 262(k)(7)(A) (Supp. IV 2010).

¹⁸³ See CONG. BUDGET OFFICE, *supra* note 169, at 1.

¹⁸⁴ *Id.* at 5.

¹⁸⁵ See generally CONG. BUDGET OFFICE, *supra* note 169. (estimates increase monotonically over time for the ten years projected from 2009 to 2018). The study identifies the increasing size of the biologic market at risk for biosimilar entry as one factor contributing to increased cost savings over time. See *id.* The size of the biologic market at risk for biosimilar entry is likely to continue to grow following 2018, and, in combination with technological advances for production of biosimilars and changes in the market acceptance of biosimilars, may result in further increases in savings. See *id.*

¹⁸⁶ Henry Grabowski et al., *Data Exclusivity for Biologics*, 10 NAT. REV. DRUGS DISCOVERY 15, 15–16 (2011).

patent expiry dates are reported in Table 3.¹⁸⁷ We find that nine top-selling biologic drugs approved through a BLA may experience the loss of key patent protection by 2016. It is unknown when these biologics may experience biosimilar market entry under BPCIA, which will depend on many technical, market, regulatory, and legal factors, whether entry will be at risk, and the outcome of patent litigation that is sure to ensue.¹⁸⁸ Table 3 lists those nine biologics, their annual U.S. sales as of 2009, and the year of the earliest publicly reported key patent expiry, as described above.¹⁸⁹ The biologics that may face patent expiry between 2012 and 2013 alone had combined 2009 U.S. revenues exceeding \$10.4 billion.

TABLE 3

*Earliest Publicly Reported Year of Potential Patent Expiry
for Selected Top-Selling Branded Biologics*¹⁹⁰

Drug	Company	2009 U.S. Sales (\$Mil)	Earliest Publicly Reported Year of Key Patent Expiry
Enbrel	Amgen	\$3,283	2012
Neupogen	Amgen	\$901	2013
Epogen, Procrit	Amgen, J&J	\$3,827	2013–2015
Rebif ¹⁹¹	Merck Serono	\$940	2013
Avonex	Biogen Idec	\$1,406	2013

¹⁸⁷ Patent expiration dates are per the manufacturers' Form 10-K and annual reports except in the cases of Rebif and Remicade, where the patent expiration dates were not reported in the companies' financial statements. For patent expiration dates for both Rebif and Remicade, the authors relied on a report prepared for the U.S. Department of Health and Human Services and confirmed those dates using alternative publicly available sources. See LEWIN GROUP & i3 INNOVUS, ECONOMIC ANALYSIS OF AVAILABILITY OF FOLLOW-ON PROTEIN PRODUCTS (July 2009) (prepared for Dep't of Health and Human Servs., Office of the Assistant Sec'y for Planning and Evaluation). Results have not been vetted with individual manufacturers. Results of future patent litigation are unknown and projected dates may change.

¹⁸⁸ Other top-selling biologic drugs, including Humalog, Novolog, and Lantus, may lose protection from key patents by 2016, but were approved through NDAs.

¹⁸⁹ Results have not been vetted with individual manufacturers. The results of future patent litigation are unknown, and therefore projected dates may change.

¹⁹⁰ The potential year of patent expiry reflects company financial report disclosures when available and are supplemented with analyst reports and other public sources. Results have not been vetted with individual manufacturers. Results of future patent litigation are unknown and projected dates may change. See also *supra* note 187.

¹⁹¹ The BLA for Rebif received FDA approval in 2002, indicating that the 12-year component of NBE exclusivity will end in 2014.

Drug	Company	2009 U.S. Sales (\$Mil)	Earliest Publicly Reported Year of Key Patent Expiry
Remicade ¹⁹²	Johnson & Johnson	\$3,088	2014–2018
Neulasta	Amgen	\$2,527	2015
Rituxan ¹⁹³	Biogen Idec	\$2,666	2015–2018
Humira ¹⁹⁴	Abbott	\$2,519	2016–2018

VI. INNOVATION INCENTIVES

As with the Hatch-Waxman Act, Congress attempted to balance the objectives of achieving cost savings from an abbreviated pathway for biosimilars with preserving innovation incentives for new biologics. The law differs from Hatch-Waxman in the length of the exclusivity period for innovators: the BPCIA establishes twelve years after the approval of an innovative biologic during which the FDA cannot approve a biosimilar referencing it, versus the Hatch-Waxman Act, which establishes five years after approval of a NCE during which an abbreviated application for a generic drug referencing the NCE cannot be submitted.¹⁹⁵ Furthermore, as discussed earlier, the process for resolving patent disputes is very different for biologics under the BPCIA than for new chemical entities under Hatch-Waxman. This Part considers the growing importance of biological innovation for the healthcare sector, the innovation process in biotechnology, and how the provisions of the new law are expected to affect innovation incentives.

A. *The Importance of Pharmaceutical Innovation*

The biotech industry is a relatively new source of medical innovation with its first new drug product approvals coming in the early 1980s. It has, however, become a major source of novel drug introductions and overall industry growth in recent years. Grabowski and Y. Richard Wang examined the quantity and quality of new drug introductions worldwide between 1982 and 2003 and found that biotech drugs are the fastest growing segment of new therapeutics, accounting for 4% of new drug introductions in the 1982 to 1992

¹⁹² The manufacturer relies on MAb technology that may be protected by Genentech's Cabilly II patent until the year 2018, subject to ongoing litigation. The extent to which licensing this MAb technology protects against biosimilar entry is uncertain.

¹⁹³ *Id.*

¹⁹⁴ *Id.*

¹⁹⁵ Compare 42 U.S.C. § 262(k)(7)(A) (Supp. IV. 2010), with 35 U.S.C. § 156(d)(5)(E)(i) (Supp. IV 2010).

period, but increasing to 16% in the 1993 to 2003 period.¹⁹⁶ U.S. firms are the dominant source of biotech drugs, originating more than half of all worldwide biopharmaceutical introductions from 1982 to 2003.¹⁹⁷

One of the key indicators of drug quality or novelty in the study was whether the entity was a first-in-class introduction. New biological entities had a significantly higher likelihood of being a first-in-class or novel introduction compared to new drug introductions.¹⁹⁸ New biologics have been particularly focused on oncology and immunology in recent years. In particular, the oncology class has recently experienced the introduction of breakthrough monoclonal antibodies and targeted biological agents resulting from increased knowledge of the molecular mechanisms for cancer—these breakthrough products include rituximab (Rituxan), trastuzumab (Herceptin), and bevacuzimab (Avastin).¹⁹⁹

Several new biological entities have had rapid diffusion and are among the leading drug therapies in their class. Substantial improvements in survival, morbidity, and patients' quality of life have been documented in diseases previously resistant to successful treatment, including cancers such as aggressive HER-2 positive breast cancer.²⁰⁰ Improvements were also made in the prevention of disease progression, functional decline, joint destruction, and disability associated with rheumatoid arthritis.²⁰¹

The prospects of future advances are further enhanced by a robust pipeline of more than 600 biotech drugs under development in a variety of therapeutic areas.²⁰² These include novel approaches to

¹⁹⁶ Henry Grabowski et al., *The Quantity and Quality of Worldwide New Drug Introductions 1992-2003*, 25 HEALTH AFFS. 452, 458 (2006).

¹⁹⁷ *Id.*

¹⁹⁸ *Id.*

¹⁹⁹ Joseph A. DiMasi & Henry G. Grabowski, *The Economics of New Oncology Drug Development*, 25 J. CLINICAL ONCOLOGY 209, 214–15 (2007).

²⁰⁰ Ian Smith et al., *2-Year Follow-Up of Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Breast Cancer: A Randomized Controlled Trial*, 369 THE LANCET 29, 33 (2007).

²⁰¹ See generally A.L. Weaver, *The Impact of New Biologics in the Treatment of Rheumatoid Arthritis*, 43 RHEUMATOLOGY iii17 (2004) (describing studies on the impact of biologics in the treatment of rheumatoid arthritis).

²⁰² See PhRMA, 2008 REPORT: MEDICINES IN DEVELOPMENT—BIOTECHNOLOGY: BIOTECHNOLOGY RESEARCH CONTINUES TO BOLSTER ARSENAL AGAINST DISEASE WITH 633 MEDICINES IN DEVELOPMENT 1 (2008), available at <http://www.phrma.org/sites/default/files/422/biotech2008.pdf>.

conditions with large unmet medical need and societal disease burdens, including more than 250 biotech drugs for cancer alone.²⁰³

John Calfee and Elizabeth DuPré have identified two important features of competition involving new biological entities.²⁰⁴ First, after proof of principle has been established for a new biological, multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate target (e.g., a particular receptor or dysfunctional enzyme).²⁰⁵ In the case of Herceptin, for example, in 2008 there were fifty-one molecular targeted therapies in Phase II or III trials for breast cancer, many targeting the HER-2 receptor, other members of the HER family, or one of the other proteins downstream from HER-2.²⁰⁶ The tumor necrosis factor inhibitors for rheumatoid arthritis and the angiogenesis inhibiting drugs for cancer are also experiencing similar forms of competition involving the same-targeted pathways, but with different specific modes of action.²⁰⁷

A second important feature of competition for new biological entities involves new indications associated with the same or related pathways.²⁰⁸ For example, drugs initially approved for rheumatoid arthritis have been, or are being, investigated for a number of anti-inflammatory conditions that may be related to the same dysfunctional pathway. Two of the leading rheumatoid arthritis drugs have already received subsequent approval for psoriasis (Enbrel) and Crohn's disease (Remicade).²⁰⁹ Michael Flanagan finds that as of the mid-2000s Avastin had 15 Phase III and 105 Phase II clinical trials in progress for more than twenty different types of cancer and different stages of cancer.²¹⁰

²⁰³ *Id.*

²⁰⁴ John E. Calfee & Elizabeth DuPré, *The Emerging Market Dynamics of Targeted Therapeutics*, 25 HEALTH AFFS. 1302, 1305–06 (2006).

²⁰⁵ *Id.* at 1306.

²⁰⁶ DATAMONITOR, PIPELINE INSIGHT: BREAST CANCER—RECENT APPROVALS INCREASE PRESSURE ON PIPELINE CANDIDATES 4 (Apr. 2008); *see generally* Laura Tookman & Rebecca Roylance, *New Drugs for Breast Cancer*, 96 BRIT. MED. BULL. 111 (2010) (discussing the targeted drug therapies for HER-2 positive breast cancer, including trastuzumab).

²⁰⁷ DATAMONITOR, PIPELINE INSIGHT: DISEASE MODIFICATION IN RHEUMATOID ARTHRITIS—NEW DRUG TARGETS COMPETE IN CROWDED MARKET 67 (Oct. 2009).

²⁰⁸ Calfee & DuPré, *supra* note 204, at 1306.

²⁰⁹ *Id.* at 1307.

²¹⁰ M. Flanagan, *Avastin's Progression*, BIOCENTURY, March 6, 2006, at A4.

B. NBE Exclusivity and Patent Protection

The process of discovering and developing a new biologic is a long, costly, and risky venture. Joseph DiMasi and Grabowski have estimated that the development of a typical new biologic costs \$1.2 billion in capitalized R&D costs.²¹¹ This compares with an earlier study of the cost of an NCE, estimated at roughly \$800 million.²¹² DiMasi and Grabowski found that biologics cost more in the discovery phase, take longer to develop, and require greater capital investment in manufacturing plants.²¹³ They found that the probability of success is higher for biologics than NCEs, but biologics that fail do so later in the R&D life cycle.²¹⁴ After adjustment for inflation and the different time periods studied, the cost of developing a biologic and an NCE are roughly comparable in value.²¹⁵

The development of new medicines requires large and risky up-front capital investments. Intellectual property protection in the form of patents and exclusivity provisions in the BPCIA and Hatch Waxman Acts (“NBE/NCE exclusivity periods”) are the primary policy instruments used in the United States with the aim of allowing investors to recoup sufficient profits from successful innovations to encourage risky investment in R&D for new medicines.²¹⁶ NBE/NCE exclusivity and patents have separate but complementary roles. The U.S. government awards patents for inventions based on well-known criteria: novelty, utility, and non-obviousness.²¹⁷ Patents are the main policy instrument for encouraging invention of, and innovation in, new products in the U.S. economy. NBE/NCE exclusivity, including data exclusivity, which protects investment in safety and efficacy data from use or reference by others in their abbreviated applications for a period of time, and market exclusivity, which prohibits competitors from marketing for a period of time, recognizes that after invention—typically before clinical trials—a long, risky, and costly R&D process remains in the United States for the development of new

²¹¹ Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 *MANAGERIAL & DECISION ECON.* 469, 475 (2007).

²¹² Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 *J. HEALTH ECON.* 151, 166 (2003).

²¹³ DiMasi & Grabowski, *supra* note 211, at 473, 477.

²¹⁴ *Id.* at 472, 473 fig.1.

²¹⁵ *Id.* at 477.

²¹⁶ Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 *NAT. REVS. DRUG DISCOVERY* 479, 479–87 (2008); *see also* Grabowski et al., *supra* note 186, at 15–16.

²¹⁷ Grabowski, *supra* note 216, at 479.

medicines.²¹⁸ Effective patent life is often uncertain because significant patent time elapses before FDA approval and because there is uncertainty associated with the resolution of any patent challenges.²¹⁹ As a result, NBE/NCE exclusivity provides a more predictable period of protection. It essentially acts as an “insurance policy” in instances where patents are narrow, uncertain, or near expiry.

The protection afforded by NBE exclusivity may be particularly important for innovation incentives in biologics because some have asserted that patents in biologics may be either narrower in scope than those for small-molecule drugs or potentially at greater risk of being successfully challenged or circumvented.²²⁰ Biologics often rely only on formulation, or process, patents.²²¹ Given that a biosimilar will be slightly different in its composition and/or manufacturing process, a court may determine that it does not infringe the innovator’s patent.²²² This has the potential to lead to a seemingly contradictory outcome where a biosimilar may be “different enough” not to infringe the innovator’s patents, but, on the other hand, it may be “similar enough” to qualify for approval through an abbreviated approval pathway.²²³

C. *Economic Insights Regarding a Reasonable NBE Exclusivity Period*

The new law grants twelve years of exclusivity for innovative biologics during which the FDA may not approve biosimilars referencing them, compared to five years of exclusivity for NCEs under the Hatch-Waxman Act during which an abbreviated application referencing them cannot be submitted (plus a stay on generic entry of up to thirty months when there is a patent challenge to allow for resolution of litigation).²²⁴ By contrast, the European Union (EU) has harmonized across member states a ten-year exclusivity period for both

²¹⁸ See generally *id.* at 479–87.

²¹⁹ *Id.* at 479.

²²⁰ See e.g., Bruce S. Manheim Jr. et al., *Follow-On Biologics: Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFS. 394, 398–99 (2006).

²²¹ *See id.* at 400.

²²² *Id.* at 398–400.

²²³ *Id.* at 401.

²²⁴ *See* BPCIA, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804 (2010); Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585; U.S. DEP’T OF HEALTH & HUMAN SERVS, GUIDANCE FOR INDUSTRY: COURT DECISIONS, ANDA APPROVALS, AND 180-DAY EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2000), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072868.pdf>.

NCEs and NBEs.²²⁵ The EU also provided for an additional year of exclusivity for entities with significant new indications that are approved within the first eight years after the original molecule's approval.²²⁶

The NBE-exclusivity period was the focus of substantial debate by legislators, the 111th Congress considered bills with exclusivity periods ranging from five to fourteen years.²²⁷ To provide economic analysis to support the consideration of NBE-exclusivity periods, Grabowski developed a breakeven financial analysis using historical data on R&D costs and revenues for new biologics and the risk-adjusted market return on investment in the industry.²²⁸ Under this model, a representative portfolio of biologic candidates would be expected to "break even" (or recover the average costs of development, manufacturing, promotion, and the industry's cost of capital) between 12.9 and 16.2 years after launch.²²⁹ This analysis provided support for a NBE-exclusivity period at the longer end of the spectrum considered by legislators. It should be noted that NBE exclusivity only extends overall market exclusivity for the molecule when effective patent lifetimes are either expected to be relatively limited (because of a longer-than-average development path) or vulnerable to patent challenges or "work arounds" (given the potentially narrower scope of many biologic patents). NBE exclusivity, thus, serves as an "insurance policy" to maintain incentives for the development of promising therapeutic candidates in cases where patent protection is inadequate because of these circumstances.

In a 2009 report, the Federal Trade Commission saw little need for a NBE-exclusivity period, claiming that patents alone should be sufficient to encourage biologic innovation in most circumstances.²³⁰ Furthermore, the report argued that even when effective patent life was limited, early-mover competitive advantages should be sufficient to maintain innovation incentives, given relatively few expected biosimilar entrants, physician loyalty to the brand, and the likelihood

²²⁵ EMA, *Pre and Post-Authorisation Procedural Advice, Human Medicines*, EMEA No. CHMP/225411/2006 (July 2, 2008), available at <http://www.fdalawyersblog.com/files/EMA%20Regulatory%20and%20Procedural%20Guidance.pdf>.

²²⁶ Grabowski, *supra* note 216, at 479.

²²⁷ *Id.*

²²⁸ *Id.* at 479–88.

²²⁹ *Id.* at 486.

²³⁰ See generally FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (2009), available at <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf>.

that biosimilars will not be interchangeable with the originator's brand, as is the case with generic drugs.²³¹

To evaluate these claims, Grabowski, Long, and Mortimer, in a recent paper, extend the original model in a number of directions.²³² First, they examine how substantial brand retention of revenues after biosimilar entry affects breakeven lifetimes for innovators, assuming different market exclusivity periods. Second, using a Monte Carlo simulation approach, they examine the interaction between a NBE-exclusivity period and patent protection under different scenarios to highlight the circumstances where each is important in maintaining innovation incentives.²³³ An advantage of this simulation approach is that it allows one to consider variations in several of the model's core parameters simultaneously, such as the contribution margin and cost of capital as well as the innovator's share and price.

The results of this new analysis are generally consistent with Congress's determination that a NBE-exclusivity period that includes twelve years during which FDA may not approve a biosimilar to the innovative reference biologic, appropriately balances objectives for potential cost savings from biosimilar-price competition with long-run incentives for investment in innovative biologics.²³⁴ They find that when biologic patents are relatively less certain and expected to have shorter effective lifetimes, a NBE-exclusivity period including twelve years greatly enhances investment incentives.²³⁵ On the other hand, if biologic patents provide relatively strong protection with significant effective patent life remaining at approval, patents alone will be sufficient to maintain investment incentives in most cases.²³⁶ In those instances, however, the NBE-exclusivity period has only a minimal effect on the timing of potential biosimilar entry and consequently, on health care costs.²³⁷

One interesting question for future research is the impact disparate exclusivity periods for NCEs and NBEs will have on innovation incentives. As noted, biologic introductions and sales revenues have been growing rapidly over the last decade, and biologics have an in-

²³¹ *Id.* at iii–vi.

²³² Grabowski et al., *supra* note 186, at 15.

²³³ In their paper, Grabowski, Long, and Mortimer use the term “data-exclusivity period” to represent the same concept as the term “NBE-exclusivity period” used in this Article.

²³⁴ *Id.* at 16.

²³⁵ *Id.*

²³⁶ *Id.*

²³⁷ *Id.*

creasing presence in R&D pipelines. It remains an open question whether the longer period for NBE-exclusivity compared to NCE exclusivity will further tilt R&D incentives toward large molecules and whether Congress should revisit the NCE-exclusivity period and consider harmonizing these periods, as is currently the case in the EU.

D. The Resolution of Patent Challenges

One of the most important developments under the Hatch-Waxman generic drug framework became the importance of the paragraph IV 180-day exclusivity provisions, under which generic manufacturers could challenge the legitimacy of branded manufacturers' patents or claim that generic entry would not infringe them.²³⁸ Over time, as the law and economic benefits to generics were established, the likelihood of paragraph IV challenges increased and most drugs became subject to challenges.²³⁹ In designing the patent disclosure provisions of the new law for biologics, Congress attempted to reduce the uncertainty and economic costs associated with litigation, but it remains to be seen what the eventual effects may be and whether this objective will be met.

Under the new law, an abbreviated application for a biosimilar can be filed after four years.²⁴⁰ The filing of an application triggers a series of potentially complex private information exchanges among the biosimilar applicant, reference product sponsor, and patent owners.²⁴¹ These exchanges of information are followed by negotiations and a process for instituting litigation on the core patents when necessary. Congress has crafted these patent provisions while eliminating the incentive for litigation associated with a 180-day exclusivity period for the first filer in a successful challenge, as well as the automatic thirty-month stay on entry in Hatch-Waxman.²⁴² By instituting this potentially very complex structured process for biologics, the hope is that patent disputes will be resolved prior to the expiration of the twelve-year NBE-exclusivity period so that biosimilars can enter in a timely fashion. Whether these rules will achieve their intended effects remains unknown. Some companies have indicated that they may find it more attractive to develop evidence to support a full BLA,

²³⁸ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1586.

²³⁹ See Berndt et al., *supra* note 154, at 791.

²⁴⁰ 42 U.S.C. § 262(k)(7)(B) (Supp. IV 2010).

²⁴¹ § 262(l).

²⁴² Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585.

rather than an abbreviated biosimilar application,²⁴³ which would avoid the information disclosures about manufacturing process and formulations under the patent challenge provisions.²⁴⁴ In some cases, pursuing a full BLA instead of an abbreviated application would also allow companies to come to market in advance of the required twelve-year NBE-exclusivity period for the reference product.²⁴⁵

VII. SUMMARY AND CONCLUSIONS

The BPCIA established an abbreviated pathway for biosimilars that is expected to lead to a number of competitors for several leading biologic products over the next decade. In contrast to generic competition, there are likely to be fewer entrants into the market for particular molecules initially due to higher development, approval, and production costs, up to \$150 million for very complex biologics,²⁴⁶ compared to only a few million for generic drugs.²⁴⁷ In addition, many biosimilars are likely to be therapeutic alternatives rather than therapeutic equivalents (i.e., they will not be rated as interchangeable by the FDA).²⁴⁸ The penetration of the market will also be tempered by the reluctance of many physicians and patients to switch to biosimilars until experience in clinical settings has been established. This is likely to be particularly true for existing patients that are responding well to maintenance therapy on the reference product as well as for patients with a limited therapeutic window for successful response (e.g., certain cancer patients).²⁴⁹ Therapeutic areas with serious clinical and economic consequences associated with loss

²⁴³ See, e.g., *Sandoz Will Steer Clear of U.S. Biosimilars Pathway, Use Other Applications*, PINK SHEET, May 3, 2010, available at http://sis.windhover.com/buy/abstract.php?id=00720180006&utm_source=toc&utm_medium=website.

²⁴⁴ Michael McCaughan, *Follow-On Biologics: Is There a Pathway?*, IN VIVO BLOG (May 20, 2010, 5:30 PM), <http://invivoblog.blogspot.com/2010/05/follow-on-biologics-is-there-pathway.html>.

²⁴⁵ *Id.*

²⁴⁶ Ludwig Burger, *Battle over Biosimilar Drugs is Only for the Brave*, REUTERS (July 2, 2010), <http://uk.reuters.com/article/idUKLNE66102R20100702?rpc=401&feedType=RSS&feedName=stocksNews&rpc=401>.

²⁴⁷ See Reiffen & Ward, *supra* note 64, at 6.

²⁴⁸ See, for example, the transcripts from the FDA two-day public hearing on "Approval Pathway for Biosimilar and Interchangeable Biologic Products Public Meeting." FOOD & DRUG ADMIN. HEARING, *supra* note 30.

²⁴⁹ See *supra* Part III.B. In some therapeutic areas (e.g., immunology, oncology) physicians are unlikely to switch a patient who is responding well to a particular therapy. Similarly, the physician may have greater confidence initiating a new patient on therapies with which they have substantial experience. In the case of biosimilars it will take some time for physicians to gain experience with those particular therapies and consequently impact their choice of therapy.

of clinical effectiveness and low patient turnover are likely to experience lower rates of biosimilar penetration compared to those therapeutic areas with higher percentages of new patients—particularly, therapeutically vulnerable patients may be less likely to be prescribed biosimilars.²⁵⁰ One pivotal factor affecting the degree of entry and price competition will be the FDA requirements to receive approval as a biosimilar. Based on preliminary statements from the FDA, regulatory requirements are likely to proceed on a case-by-case basis that is science-driven and subject to change over time as the science and technology evolves.²⁵¹ Since the biosimilar industry is global and there are already biosimilars present in Europe for some leading biologic products, the extent to which foreign trials and experience are accepted by the FDA, including when the reference products differ from those in the United States, could also be an important determinant of how many biosimilars enter the U.S. market and the corresponding extent of biosimilar competition.

Another pivotal factor affecting biosimilar penetration involves the reimbursement procedures and financial incentives employed by both government and private payers to encourage biosimilar utilization.²⁵² In the case of self-injectable drugs typically managed as part of the pharmacy benefit, more cost-sensitive Medicare Part D and commercial plans are likely to employ a number of existing techniques to encourage biosimilars, including tiered formularies, prior authorization, and step-therapy requirements. In the case of biologics dispensed in physician clinics and hospitals, as infused or physician-supervised injected therapies, and typically managed as part of the medical benefit, ASP-based reimbursement algorithms under Medicare Part B and commercial plans will influence physician adoption of lower cost biosimilars.²⁵³ The statutory provision setting the six

²⁵⁰ Physicians may be all the more hesitant to experiment with a biosimilar rather than use a branded biologic, with which they have a great deal of experience, if even small differences between the brand and the biosimilar could lead to important impacts on patient health. *See supra* Part III.B.

²⁵¹ *See supra* text accompanying note 42.

²⁵² Reimbursement procedures that increase the cost of the branded biologic to the patient (e.g., coinsurance payments or copayments), constrain physician prescribing (e.g., step therapy, prior-authorization requirements), or impact the financial incentives for physicians to select one therapy over another (e.g., limitations and regulations on physicians ability to buy-and-bill infused agents) can all influence the choice of therapy and the resulting biosimilar penetration. *See supra* Part III.C.

²⁵³ Physicians may earn a margin on physician administered drugs through “buy and bill” reimbursement policies and procedures. To the extent that reimbursement policies provide financial incentives for the physician to use either the biosimilar or

percent of Medicare Part B reimbursement at an equivalent amount for both the biosimilar and the reference product will help to mitigate provider disincentives for biosimilar adoption. In addition, movement away from historical “buy and bill” physician reimbursement arrangements, including requirements that certain drugs be managed and delivered through specialty pharmacy providers, is also likely to have an important effect on the utilization of biosimilars. Coverage decisions and requirements at the regional level by Medicare contractors also could be important considerations.

The new law is designed to balance the objectives of achieving cost savings in the current period, and preserving incentives for continued innovation in the future. A number of leading biologic products with significant sales in the United States are expected to experience some patent expiration in the next decade, so cost savings could grow to meaningful values depending on how other factors such as regulation, reimbursement, and intellectual property litigation play out over this period.²⁵⁴

In terms of maintaining incentives for future innovation, the law provides for a NBE-exclusivity period in which a biosimilar can be approved utilizing an abbreviated pathway—sooner than twelve years following approval of the innovator product.²⁵⁵ NBE exclusivity provides an important “insurance policy” to the patent system and could be important in the case of biologics where patents may prove to be narrower in scope than those for new chemical entities or easier to circumvent. Analysis of a portfolio of representative biological products indicates that twelve years or more of market exclusivity from patents or NBE exclusivity is generally necessary to achieve breakeven returns that provide a risk-adjusted return on capital and R&D investments.

A number of important issues remain for future research, including how the new law will affect industry structure and incentives for undertaking R&D for biologics versus new chemical entities. As was the case with the Hatch-Waxman Act, change may be gradual at first, but over time the new law could lead to profound changes in the economics and organization of the biopharmaceutical industry.

the brand, this may impact the physician’s choice of therapy and the resulting rate of biosimilar penetration. *See supra* text accompanying notes 101–114.

²⁵⁴ *See supra* tbl.3 (illustrating biologics with combined 2009 U.S. revenues exceeding \$11.5 billion for which some key patents may expire by the end of 2013, including Enbrel, Neupogen, Epogen/Procrit, Rebif, and Avonex).

²⁵⁵ *See supra* text accompanying note 224.