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A LONGER MONOPOLY FOR BIOLOGICS?: CONSIDERING THE IMPLICATIONS OF DATA EXCLUSIVITY AS A TOOL FOR INNOVATION POLICY

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I. INTRODUCTION

The field of biopharmaceutical and biotechnology drugs, broadly referred to as "biologics," has grown dramatically over the past thirty years to comprise a major sector within the prescription drug market.[1] Biologics are drugs generally derived from living materials, including blood-derived products, vaccines, and most protein products.[2] The

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1. *See* David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 143 (2005).

2. FDA, Frequently Asked Questions About Therapeutic Biological Products, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm (follow "How Drugs

biotechnology industry has now brought to market over 254 new medicines,[3] products that account for one out of every eight prescriptions written worldwide.[4] The global market for biologics reached $75 billion in 2007,[5] and biologics sales continue to expand dramatically in relation to those for traditional small-molecule drugs.[6] In 2000, biologics accounted for eleven percent of the top 100 best-selling drugs on the market.[7] By 2014, biologics will account for seven of the top ten best-selling drugs on the market and fifty of the top 100.[8]

The increasing prevalence of biologics is also a factor in rising healthcare costs. Average per-patient treatment costs for biologics can approach twenty times that of small-molecule substitutes.[9] Annual costs regularly reach tens of thousands of dollars per patient, and in extreme cases, can rise as high as $300,000 for a year of treatment.[10] These high prices affect the cost of healthcare in the United States. For example, in 2006, Medicare Part B spent in excess of $5 billion on biologics, one of the "fastest growing segments of Medicare expenditure."[11]

One of the major factors driving the high price of biologics relative to conventional drugs is the absence of a robust industry in bio-

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are Developed and Approved" hyperlink) (last visited Dec. 20, 2009) (stating additionally that hormones such as insulin, glucagon, and human growth hormone are regulated as conventional drugs, not biological products).

3. Biotech. Indus. Org., BIO | Health | Overview, http://www.bio.org/healthcare/ (last visited Dec. 20, 2009).

4. AARP PUB. POL'Y INST., BIOLOGICS IN PERSPECTIVE 1 (2007) (citing VISIONGAIN, THE GLOBAL BIOTECH REPORT (2006)), *available at* http://assets.aarp.org/rgcenter/health/fs136_biologics.pdf.

5. Press Release, IMS Health, IMS Health Reports Global Biotech Sales Grew 12.5 Percent in 2007, Exceeding $75 Billion (June 17, 2008), http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=bba69e392879a110VgnVCM100000ed152ca2RCRD&vgnextfmt=default.

6. Saurabh Aggarwal, *What's Fueling the Biotech Engine?*, 25 NATURE BIOTECH. 1097, 1097 (2007) (noting higher growth rates for biologics compared to all pharmaceuticals and identifying sections within the biologics market responsible for the growth); Press Release, IMS Health, *supra* note 5 (reporting that global biotech sales grew at nearly double the rate of the global pharmaceutical market in 2007, in keeping with the previous five-year trend).

7. Press Release, EP Vantage, Biotech Set to Dominate Drug Industry Growth (June 17, 2009), http://www.evaluatepharma.com/Universal/View.aspx?type=Story&id=188700&sectionID=&isEPVantage=yes.

8 *Id.*

9. Press Release, Express Scripts, Inc., Biotech Drug Spending Increases 21 Percent Even as Growth in Rx Expenditure Slows (Apr. 25, 2007), http://phx.corporate-ir.net/phoenix.zhtml?c=69641&p=irol-newsArticle&ID=989907&highlight=).

10. *See* Editorial, *When a Drug Costs $300,000*, N.Y. TIMES, Mar. 23, 2008, at WK8 (discussing an example of the cost issues raised by biologics that target "ultrarare diseases").

11. Press Release, Pharmaceutical Care Management Association ("PCMA"), PCMA: Medicare Part B Program Could Save $14 Billion in Prescription Drug Costs Through Biogenerics (Jan. 4, 2007), http://www.pcmanet.org/pcma-medicare-part-b-program-could-save-14-billion-in-prescription-drug-costs-through-biogenerics/.

generics, also known as "follow-on" biologics,[12] to promote price competition in the field of biotechnology.[13] Until recently, several structural barriers have protected the biologics market from competition. Patent protection, an uncertain regulatory structure, and technological complexity have all served to shelter many of the "blockbuster"[14] products in this relatively young field.[15]

Over the next few years, some of these major barriers are poised to fall. Patents have already begun to expire on many of the first generation blockbuster biologics, including Procrit, Epogen, and Intron A.[16] Equally as important, Congress has considered several pieces of legislation (the "follow-on biologics legislation") that would eliminate some of the regulatory barriers currently preventing follow-on biologics manufacturers from obtaining market approval for competitive products.[17] Designed to replicate the approval process currently available to small-molecule generic drugs,[18] this legislation would enable follow-on biologics manufacturers to avoid costly and duplicative human clinical trials by proving that the follow-on product is comparable to the innovator drug already on the market.[19] One source estimated that this legislation has the potential to save the U.S. healthcare

12. Members of the scientific community contest the use of the term "generic biologic" because it implies that the reverse-engineered copy will be identical, or bioequivalent, to the brand name drug, which may not necessarily be true in all cases. *See* Eileen McMahon & Teresa Reguly, *Follow-On Biologics in Canada*, UPDATE, May/June 2008, at 43, *available at* http://www.torys.com/Publications/Documents/Publication%20PDFs/AR2008-42.pdf; *cf.* Press Release, PCMA, *supra* note 11 (using the term "biogeneric" to describe follow-on biologics).

13. *See* Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 439 (2007) [hereinafter Grabowski et al., *Entry and Competition*]. The manufacturing process also tends to be more expensive for biologics than for conventional drugs; consequently, even with price competition, prices of biologics may remain higher than those of conventional therapies. *See* Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1293 (2006) [hereinafter Grabowski et al., *Market for Follow-On Biologics*].

14. *See* Henry G. Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 28 MANAGERIAL & DECISION ECON. 491, 501 n.1 (2007) (defining the term "blockbuster drugs" as "new molecular entities (NMEs) with a billion dollar [sic] or more of sales in this 12 month period prior to first generic entry").

15. *See* Grabowski et al., *Entry and Competition*, *supra* note 13, at 439.

16. *Id.*

17. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575 (2009); S. Comm. On Health, Educ., Labor, and Pensions Draft Bill, 111th Cong. § 602 (2009), http://help.senate.gov/BAI09I50_xml.pdf [hereinafter Hatch Amendment]; *see also* Pathway for Biosimilars Act, H.R. 5629, 110th Cong. § 101 (2008); Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. § 2; Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2; Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3 (2007).

18. The generic approval process for small-molecule drugs was established by the Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, and 35 U.S.C.).

19. *See* H.R. 1038 § 3.

system at least $71 billion over ten years by introducing competitive follow-on biologics into the market.[20]

An abbreviated approval process for biologics could offer a number of advantages, including the potential to reduce waste from redundant trials, encourage the growth of a follow-on biologics industry, and lower the cost of treatment.[21] Yet, the possibility of such a process for approving biogenerics has sparked concern for the survival of the innovator biologics industry in the new competitive environment. The industry has lobbied Congress to incorporate a mechanism known as "data exclusivity"[22] into the new follow-on biologics legislation that would preserve incentives to innovate.[23] This protective provision would undercut the effectiveness of the legislation by preventing follow-on biologics firms from taking advantage of the streamlined approval process for at least twelve years from the date the innovator product gains regulatory approval.[24]

Whereas intellectual property rights, such as patent and copyright protection, have historically served as the primary public policy mechanism for promoting innovation in the U.S., data exclusivity is a relatively new means of protecting innovation.[25] The increasing use of data exclusivity as a tool for innovation policy in the pharmaceutical industry raises two key concerns: first, the ongoing effectiveness of the patent system for promoting drug innovation, and second, the need to determine the best mechanism for balancing innovation and access

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20. Steve Miller & Jonah Houts, EXPRESS SCRIPTS, INC., POTENTIAL SAVINGS OF BIOGENERICS IN THE UNITED STATES 1 (2007), http://www.expressscripts.com/industryresearch/outcomes/onlinepublications/study/potentialSavingsBiogenericsUS.pdf.

21. *See* Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics Under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 103 (2007) (describing how abbreviated approval could reduce waste and make low-cost drugs available); *see also* A. Taylor Corbitt, *The Pharmaceutical Frontier: Extending Generic Possibilities to Biologic Therapies in the Biologics Price Competition and Innovation Act of 2007*, 18 DEPAUL J. ART, TECH. & INTELL. PROP. L. 365, 390–91 (2008) (discussing the feasibility of applying a generic approval framework to the biologics industry).

22. Data exclusivity is a time period after the approval of a new product during which competitors cannot gain regulatory approval by relying on the fact that safety and effectiveness has already been established for the innovator product. *See infra* Part II.B. During the data exclusivity period, the clinical and other test data used to gain pre-market approval of the innovator product is "exclusive" in the sense that firms wishing to have identical products approved must generate their own independent data. *See id.*

23. *See* Press Release, Biotech. Indus. Org., BIO Calls for 14 Years of Data Exclusivity in Any Follow-On Biologics Legislation (May 3, 2007), http://www.bio.org/news/pressreleases/newsitem.asp?id=2007_0503_01 (defining data exclusivity as "the time period after approval of the innovator's product during which the Food and Drug Administration may not approve a follow-on biologic. . . relying to any degree on the safety and effectiveness of the innovator product").

24. *See, e.g.*, H.R. 5629, 110th Cong. § 101 (2008) (proposing a twelve-year period of data exclusivity); H.R. 1956, 110th Cong. § 2 (2007) (proposing up to a fifteen-year period of data exclusivity).

25. Data exclusivity was first introduced in the 1984 Hatch-Waxman Act. *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 359–60 (2007).

in an industry undergoing dramatic change. This Note will explore these issues and the implications of data exclusivity for innovation policy in the U.S.

Part II details the need for a more efficient abbreviated regulatory approval pathway for follow-on biologics and explains how data exclusivity could block access to this new pathway in an effort to promote innovation. Part III describes the ways in which patent law currently leaves gaps in protection, failing to provide incentives to develop promising new products. It also evaluates some of the potential risks associated with expanding monopoly protection to fill these gaps. Part IV assesses mechanisms that could be implemented to supplement the patent system, identifies data exclusivity as the most likely legislative response to current failures, and considers ways in which a data exclusivity provision might be tailored to play this role effectively while avoiding the creation of unnecessary costs and misaligned incentives. Part V concludes.

II. UNIQUE REGULATORY TREATMENT OF BIOLOGICS

Biologics constitute a broad and imperfectly defined regulatory category. Section 351 of the Public Health Service Act ("PHSA") defines a biological product by a list of product types: a biologic may be "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[26] Most biological products covered under the PHSA also meet the definition of new drugs under the Food, Drug, and Cosmetics Act ("FDCA").[27] The Food and Drug Administration ("FDA"), the agency charged with regulating biologics,[28] has not always arrived at clear or consistent results when endeavoring to fit novel products into the statutory definition of "drug" or "biological product." For example, some of the first recombinant protein-based therapeutics derived from human and animal material, including hormones such as insulin and human growth hormone, are actually regulated as new drugs under the FDCA.[29] Yet, since 1991, all newly

26. Public Health Service Act § 351, 42 U.S.C. § 262(i) (2006).

27. *See* Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified at 21 U.S.C. § 321(g)(1) (2006)) (defining the term "drug"); FDA, Center for Biologics Evaluation and Research — Responsibilities, Questions and Answers, http://www.fda.gov/aboutFDA/Centersoffices/cber/ucm133072.htm (last visited Dec. 20, 2009).

28. FDA, About FDA — What We Do, http://www.fda.gov/AboutFDA/WhatWeDo/default.htm (last visited Dec. 20, 2009).

29. *See* Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 368 (1996).

approved protein products have been regulated as biological products under the PHSA.[30]

A. The Need for a More Efficient Regulatory Approval Pathway

The unique regulatory treatment of biological products preserves barriers to market entry for follow-on biologics that do not exist for generic drugs. A biologics licensing application ("BLA") is a prerequisite to bringing a biological product to market.[31] The BLA is similar to the required New Drug Application ("NDA") for conventional drugs.[32] Currently, firms wishing to introduce competing follow-on biologics to the market must submit their own independent BLA. To receive a license, an applicant must conduct extensive animal tests and human clinical trials documenting the safety, purity, and potency of the follow-on product.[33]

Under the Hatch-Waxman Act of 1984,[34] producers of small-molecule generics may gain approval by submitting an Abbreviated New Drug Application ("ANDA"). Rather than include independent evidence of safety and effectiveness, the ANDA need only prove that the generic drug is interchangeable, or bioequivalent, with a brand name drug already on the market.[35] Manufacturers of small-molecule generics can thus avoid needless and potentially unethical efforts to duplicate the animal testing and human clinical trial results already achieved by the producer of the original, reference product.[36]

Commentators have suggested that existing law authorizes the FDA to employ the ANDA process in approving follow-on biologics.[37] However, the FDA has consistently refused to allow biologics

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30. FDA, Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research III (B)(1)(f) (Oct. 31, 1991), http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm (excluding antibiotics and protein products previously approved as drugs).

31. *See* 42 U.S.C. § 262(a); 21 C.F.R. § 601.2 (2009).

32. *See* James N. Czaban & Natasha Leskovsek, *FDA Regulation of Biological Products*, *in* THE PHARMACEUTICAL REGULATORY PROCESS 73, 74 (Ira R. Berry ed., 2005).

33. *See* 21 C.F.R. § 601.2(a) (listing requirements to obtain a BLA); *Follow-on Protein Products: Hearing Before the H. Comm. on Oversight and Gov't Reform*, 110th Cong. 20 (2007) (statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, FDA) [hereinafter *Follow-on Protein Products Hearing*] (stating that there is no abbreviated approval pathway for biological products regulated under the PHSA).

34. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, and 35 U.S.C.).

35. 21 U.S.C. § 355(j) (2006); § 505(j), 98 Stat. at 1585.

36. Dudzinski, *supra* note 1, at 194 (citing H.R. REP. NO. 98-857, at 16 (1984)) (describing the requirement of conducting placebo-controlled human clinical trials for generic drugs as unnecessary, wasteful, and unethical where it denies sick patients an effective treatment). Clinical trials need not always include a placebo or non-treatment group. *See infra* note 62.

37. Dinh, *supra* note 21, at 77.

regulated under the PHSA to take advantage of the ANDA process,[38] voicing concern that bioequivalence may be difficult to prove for biological products that are potentially more complex than small-molecule drugs.[39] Commentators have criticized the FDA's cautious treatment of biologics as antiquated when applied to a field that now includes drugs manufactured through controlled biosynthetic processes that may be accurately characterized and reproduced.[40] The FDA's own actions also demonstrate that clinical trials are not always necessary to prove that copies made through a new process are safe to bring to market. The FDA has long allowed producers of brand name biologics to modify their manufacturing processes, relying on analytic tests — as opposed to full-scale clinical trials — to show that the products manufactured using the new process have the same safety, identity, purity, and potency as the reference products.[41] There is a growing consensus that an adequate abbreviated approval process can be similarly designed for follow-on biologics.[42]

The most recent legislative proposals concerning follow-on biologics were introduced by Senator Orrin Hatch (R-UT) (the "Hatch Amendment")[43] and Representative Anna Eshoo (D-CA) (the "Eshoo Amendment")[44] into two versions of the 2009 Health Care Reform

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38. In 2006, the D.C. District Court required the FDA to review a FDCA § 505(b)(2) abbreviated application for the recombinant protein Omnitrope, a growth hormone regulated as a drug under the FDCA. Sandoz, Inc. v. Leavitt, 427 F. Supp. 2d 29, 33 (D.D.C. 2006). The FDA has since distinguished Omnitrope from other protein products, stating that abbreviated approval will not be available to protein products regulated under the PHSA. Internet Archive, FDA Omnitrope (somatropin) Questions and Answers (Feb. 23, 2008), http://web.archive.org/web/20080223133945/http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm (stating that "there is no abbreviated approval pathway . . . for protein products licensed under section 351 of the [PHSA]").

39. *Follow-on Protein Products Hearing*, *supra* note 33, at 20 (statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, FDA).

40. Dudzinski, *supra* note 1, at 186–87.

41. *See* Ctr. for Biologics Evaluation & Research & Ctr. for Drug Evaluation & Research, Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (1996), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm.

42. *See, e.g.*, Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 590–609 (2008); Jeremiah J. Kelly & Michael David, *No Longer "If," But "When": The Coming Abbreviated Approval Pathway for Follow-on Biologics*, 64 FOOD & DRUG L.J. 115, 121 (2009).

43. *See* Posting of Kurt R. Karst to FDA Law Blog, Senate HELP Committee Passes Amendment for 12-Year Biologics Exclusivity Period, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/07/senate-help-committee-passes-amendment-for-12year-biologics-exclusivity-period.html (July 14, 2009, 5:39 EDT).

44. *See* Posting of Kurt R. Karst to FDA Law Blog, House Energy & Commerce Committee Reports Health Care Reform Bill with FOB and "Pay-for-Delay" Provisions, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/08/house-energy-commerce-committee-reports-health-care-reform-bill-with-fob-and-payfordelay-provisions.html (Aug. 2, 2009, 13:02 EDT).

Legislation.[45] Following the Hatch-Waxman Act's ANDA model, each amendment would allow the producer of a follow-on biological product to gain regulatory approval by making comparisons with a reference product that is already approved. Rather than showing bioequivalence, biologics must show that the follow-on product is "biosimilar" to the reference product.[46] A biosimilar product must be "highly similar" to the reference product and have "no clinically meaningful differences . . . in terms of the safety, purity, and potency of the product."[47] This slightly more flexible requirement of similarity, rather than sameness, will come at a price: pharmacists will generally not be permitted to substitute biosimilar products without consulting the prescribing physician, as is the common practice with generic small-molecule drugs.[48] In order for such substitutions to occur, the follow-on product must be deemed "interchangeable" with the reference product; "interchangeability" is a higher standard requiring that the two products have identical risk profiles.[49]

B. The Data Exclusivity Controversy

Data exclusivity was first introduced in the United States in 1984 as part of the Hatch-Waxman Act.[50] The Hatch-Waxman Act applies a five-year data exclusivity term to approvals of all drugs containing new active ingredients.[51] The provision delays entry of generic drugs by creating a period during which manufacturers of generics cannot gain regulatory approval by submitting an ANDA that references the market approval of the innovator drug, sometimes called the "reference" product.[52] The period runs for five years from the date of regulatory approval of the innovator drug.[53] The innovator may also apply for three additional years of data exclusivity on approvals for changes

45. Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575 (2009); Hatch Amendment § 602.

46. H.R. 3962 § 2575(a)(2) (amending 42 U.S.C. § 262(k)(2)(A)(i)(I)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(2)(A)(i)(I)).

47. H.R. 3962 § 2575(b)(3) (amending 42 U.S.C. § 262(i)(2)(B)); Hatch Amendment § 602(b)(3) (amending 42 U.S.C. § 262(i)(2)(B)).

48. H.R. 3962 § 2575(b)(3) (amending 42 U.S.C. § 262(i)(3)); Hatch Amendment § 602 (b)(3) (amending 42 U.S.C. § 262(i)(3)).

49. H.R. 3962 § 2575(a)(2) (amending 42 U.S.C. § 262(k)(4)); H.R. 3962 § 2575(b)(3) (amending 42 U.S.C. § 262(i)(2)(B)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(4)); Hatch Amendment § 602(b)(3) (amending 42 U.S.C. § 262(i)(2)(B)).

50. *See* Eisenberg, *supra* note 25, at 359–64 (describing the history of data exclusivity along with similar FDA-administered exclusivity periods).

51. 21 U.S.C. § 355(j)(5)(F)(ii) (2006) (requiring that the product be "a drug, no active ingredient . . . of which has been [previously] approved in any [new drug] application" to qualify for five-year exclusivity).

52. *Id.*

53. *Id.* However, the ANDA may be submitted four years after the NDA if it contains a Paragraph IV certification. *Id.* § 355(c)(3)(E)(ii); *see infra* note 79 (describing Paragraph IV certifications).

to the drug, such as new uses or dosage forms, which require submission of new clinical data.[54] In such cases, the additional three-year exclusivity applies only to the modified version or new use of the product, leaving follow-on firms free to seek approval for copies of the original drug once the initial five-year period and related patents have expired.[55]

With many of the safety issues concerning follow-on biologics resolved, data exclusivity remains one of the most contentious aspects of the proposed legislation, which has stalled in Congress for two successive years.[56] The Hatch and Eshoo Amendments contain provisions that would grant a minimum of twelve years of exclusivity to newly approved biological products, with the potential to gain an additional twelve years of protection on each new improvement to the product that involves a structural change.[57] These twelve-year periods and twelve-year extensions currently under consideration by Congress offer considerably more protection to biologics than the five- and three-year periods provided to small-molecule drugs under the Hatch-Waxman Act.

While the exclusivity term runs, follow-on firms would be prohibited from making reference to data submitted by the innovator firm in obtaining its license to market the reference product.[58] In other words, beginning at the point of FDA approval of the reference product, firms wishing to produce follow-on biologics would be unable to use the abbreviated approval pathway for the length of the data exclusivity term. Manufacturers of follow-on biologics would be forced to submit an independent BLA, which would in turn require them to generate independent clinical data.

The data exclusivity period would function to protect the innovator from price competition by creating financial barriers to entry for follow-on firms. Generation of clinical trial data amounts to more than

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54. *Id.* § 355(j)(5)(F)(iii)–(iv).

55. *See* Eisenberg, *supra* note 25, at 359–60.

56. *See* Press Release, Senator Charles Schumer, Waxman, Schumer, and Clinton Unveil Bill to Create Clear Pathway for Generic Biologic Drugs (Feb. 14, 2007), http://schumer.senate.gov/new_website/record.cfm?id=269733 (introducing the first follow-on biologics bill); *see also* Generic Drugs Business Editors' Blog, Battle Lines Drawn Over Data Exclusivity, http://genericdrugsbusiness.blogspot.com/2009/08/battle-lines-drawn-over-biologic-data.html (Aug. 14, 2009, 11:22 EDT) (describing the contentious debate over data exclusivity); Posting of Kurt R. Karst, *supra* note 43 (discussing data exclusivity in various proposals).

57. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575(a)(2) (2009) (amending 42 U.S.C. § 262(k)(7)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(7)); *see also infra* note 138 (describing the scope of availability for the twelve-year extensions).

58. *See* H.R. 3962 § 2575(a)(2) (amending 42 U.S.C. § 262(k)(7)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(7)).

half of the total cost of gaining FDA approval for a new drug.[59] The trials are time consuming, requiring an average of eight years to complete in the case of biologics.[60] Running a placebo-controlled trial of a follow-on version of a drug already on the market raises ethical challenges,[61] and the existence of the innovator product can also increase the costs of a trial by slowing the process of recruiting new subjects.[62] A follow-on firm could still conceivably design and carry out an ethical clinical trial,[63] gain independent market approval, and enter the market before the data exclusivity period expires. However, this expensive process would yield reduced rewards, as the follow-on firm would then have to compete both with the innovator firm and with other follow-on producers entering the market after the expiration of the exclusivity period. Consequently, data exclusivity effectively functions similarly to the exclusionary right in patent law; it impedes competitors' entry into the market, creating an artificial scarcity that allows the innovator to raise the price of the protected product.

III. THE NEED FOR A CHANGE IN INNOVATION POLICY

The heated debate over data exclusivity takes place in a context of mounting pressures for patent reform. Even critics of the patent system generally concede that the pharmaceutical industry is one industry in which patent rights offer innovator firms a substantial benefit by

59. A 2003 study estimated that the total clinical costs for an approved new drug are $749 million. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 165 (2003) (estimating that $282 million of clinical costs are expensed immediately, whereas $467 million are capitalized). Total preapproval costs were estimated to be approximately $1.2 billion. *Id.* at 173 (estimating that $403 million of these costs are expensed immediately, whereas $802 million are capitalized). Thus, according to this study, total clinical costs comprise approximately sixty-two percent of total preapproval costs.

60. Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 473 (2007) (estimating the clinical development period for new biological products).

61. For example, the welfare of an ill patient would be harmed by offering them an inactive placebo when a safe and effective treatment is available. The FDA requires an institutional review board to assess all trials of biologics that use human subjects to protect the rights and welfare of the participants. *See* 21 C.F.R. §§ 56.101, 601.2(a) (2009).

62. Sick patients with existing treatment options are less likely to volunteer for clinical trials of an unproven treatment, particularly one that purports to be identical to present options. The additional time needed to find new subjects for clinical research raises capitalized costs, which account for more than half of total clinical costs. *See* DiMasi et al., *supra* note 59, at 165.

63. The FDA allows trials to include an active treatment control group, within which patients would receive a known effective therapy. 21 C.F.R. § 314.126(b)(2)(iv). There may be persistent ethical issues associated with unnecessary animal and human testing, particularly toxicity trials involving healthy subjects, but these ethical issues likely will not prevent an institutional review board from granting approval to the trial.

protecting goods that are difficult to create but easy to copy.[64] Certain features of the patent system in the pharmaceutical context have nevertheless led to increasing pressure for industry-specific innovation policy reform.[65]

A. Concerns for Innovators

One of the most important patent reform issues relates to the coverage and duration of the patent right. The end of the patent term is linked to the patent filing date.[66] A drug becomes patentable when a promising new use is first discovered in a laboratory setting.[67] Title 35 of the United States Code, which covers patents, contains provisions requiring the inventor to apply for a patent soon after this discovery.[68] The twenty-year patent term begins to run at the point the patent application is filed.[69] As the patent clock ticks, the makers of new biological products and new drugs must hurry to conduct tests and obtain regulatory approval from the FDA so that they can begin marketing the product in the United States.[70] The average length of time required for this clinical development process has recently been estimated at 7.5 to 8 years.[71] Thus, a substantial number of years can elapse between the point at which the patent term begins and the point at which the drug reaches the first consumer, shortening the time during which innovators can exploit their patents by selling at monopoly prices.[72]

The Hatch-Waxman Act attempted to correct for this shortening of the effective patent life by allowing additional years at the end of a drug's patent term to make up for part of the time lost during regula-

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64. *See, e.g.*, JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE 16 (2008); Natasha N. Aljalian, *The Role of Patent Scope in Biopharmaceutical Patents*, 11 B.U. J. SCI. & TECH. L. 1, 9–11 (2005).

65. *See* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1633–34 (2003) (naming the biotechnology and software industries as the two industries that have been the most vocal in calling for specific, industry-tailored patent legislation).

66. *See* 35 U.S.C. § 154(a)(2) (2006) (establishing a patent term of twenty years from the date of filing).

67. A product or process can become patentable before a drug is tested on humans. *See, e.g.*, *In re* Brana, 51 F.3d 1560, 1562–63, 1568 (Fed. Cir. 1995) (holding that a product had met the utility requirements when the compound in question inhibited tumor models in mice and affected human tumor cells in an artificial environment). "The stage at which an invention in [the field of medical innovations] becomes useful [for the purposes of patentability] is well before it is ready to be administered to humans." *Id.* at 1568.

68. *See* 35 U.S.C. § 102(b)–(d) (describing exceptions to patentability where the inventor makes certain delays in filing a patent application).

69. 35 U.S.C. § 154(a)(2).

70. *See supra* text accompanying notes 32–33 (describing the clinical trials requirement); 59–60 (describing the costs of such trials).

71. DiMasi & Grabowski, *supra* note 60, at 473.

72. *Cf.* Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L J. TECH. MGMT. 98, 103 (2000) (noting that the duration of clinical testing and regulatory review periods has increased to approximately eight years).

tory approval.[73] These extensions, which were codified in Title 35, are available to small-molecule drugs and biologics alike.[74] As a result of these extensions, the average potential patent life for new drugs has increased substantially over the past twenty years.[75] Yet, the extensions account only for parts of the regulatory review period[76] and do not make up for all of the time lost during product development. In fact, one group of researchers has estimated that the actual period of monopoly pricing enjoyed by manufacturers of new drugs may be decreasing, at least for the most profitable "blockbuster" products.[77] In rare cases, a drug may not even reach the market until after the original patent has expired.[78]

Patent challenges add further uncertainty on the tail end of the patent term. The Hatch-Waxman Act encourages such challenges by rewarding the first generic firm to submit an ANDA challenging the patent.[79] The first generic challenger receives a 180-day period of exclusivity during which the FDA will not review subsequent ANDAs.[80] Best-selling small-molecule drugs currently subject to this provision are almost guaranteed to face a challenge before the end of the patent term.[81] Patent challenges are likely to pose a similar concern for bio-

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73. 35 U.S.C. §§ 155–56.

74. *See* 35 U.S.C. § 156(f)(2)(A) (including "human biological product" within the scope of the patent-extension provision).

75. NAT'L INST. FOR HEALTH CARE MGMT. FOUND., PRESCRIPTION DRUGS AND INTELLECTUAL PROPERTY PROTECTION 3 (2000), http://www.nihcm.org/~nihcmor/pdf/prescription.pdf.

76. 35 U.S.C. § 156(c) (listing various parts of the period that are discounted by one-half and capping the total extension at fourteen years).

77. Grabowski & Kyle, *supra* note 14, at 491.

78. *See* Eisenberg, *supra* note 25, at 352 n.27 (explaining that the patents covering a class of compounds brought to market in 1993 under the brand name *Paxil* expired on October 14, 1992, prior to FDA approval of the drug).

79. *See* 21 U.S.C. § 355(j)(5)(B)(iv) (2006). These challenges are referred to as "Paragraph IV" certifications because they require a certification of patent invalidity or noninfringement under Paragraph IV of the relevant part of the statute. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (allowing generic sponsors submitting an ANDA to certify that any unexpired patents not listed by the sponsor of the reference product are invalid or will not be infringed by the generic product).

80. *See* 21 U.S.C. § 355(j)(5)(B)(iv) (offering 180-day reward to successful challengers).

81. Of the ten best-selling conventional drugs of 2008, nine faced patent challenges from generic entrants. IMS Health reported that the top-selling drugs for 2008 were Lipitor, Nexium, Plavix, Advair Diskus, Seroquel, Singulair, Actos, Prevacid, Abilify, and Effexor XR. IMS Health, Top U.S. Pharmaceutical Products by Sales, http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Global_Top_15_Products.pdf (list excludes top-selling biologics Enbrel, Remicade, Neulasta, and Epogen). According to the FDA list of Paragraph IV Patent Certifications as of November 5, 2009, several of these drugs have faced patent challenges under Paragraph IV. *See* FDA, Paragraph IV Patent Certifications (Nov. 5, 2009), http://www.fda.gov/downloads/Drugs/DevelopmentApprova-Proess/HowDrugsareDevelopedandAproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM154350.pdf (listing Paragraph IV challenges for Lipitor, Nexium, Plavix, Seroquel, Singulair, Actos, Prevacid, Abilify, and Effexor).

logics manufacturers under the new regulatory regime, as the Hatch and Eshoo Amendments,[82] like previous versions of the follow-on biologics legislation,[83] each include a system to encourage early patent challenge.

B. Bad Patents for Good Products: The Need for Alternative Innovation Incentives

Data exclusivity provides market protection to newly approved products irrespective of whether the products are under patent.[84] Yet firms with strong patent protection will not actually benefit from data exclusivity because their patents already allow them to maintain a monopoly on the market. Only in circumstances where a patent is expired or where a weak patent is likely to be found invalid or non-infringed can data exclusivity provide a benefit to innovators.

Should firms whose patents would fail in court be entitled to market protection? If the patent system is working as intended, the answer is "no." The requirements of patent law have been carefully tailored to ensure that the government-imposed market barrier is only granted to those who have earned the reward by giving something of value back to society.[85] As Justice O'Connor has explained, "[the] requirements of patentability embody a congressional understanding, implicit in the Patent Clause itself, that free exploitation of ideas will be the rule, to which the protection of a federal patent is the exception."[86] If the patent system is working properly, the exclusivity right should be denied in cases where firms have failed to live up to their end of the patent bargain. It would be wrong to allow firms whose patents would not

82. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575(a)(2) (2009) (amending 42 U.S.C. § 262(k)(6)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(6)).

83. *See, e.g.*, Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. § 3(a)(2) (2009).

84. This is because all newly approved products are entitled to a standard exclusivity period upon approval by the FDA regardless of whether the product is patented. *See, e.g.*, 21 U.S.C. § 355(j)(5)(F)(ii) (granting five-year period for new active ingredients); H.R. 3962 § 2575(a)(k)(7) (proposing a twelve-year period for all biological products). One minor variation to this arrangement for small-molecule drugs is that where patents exist on the product, generic entrants may apply for abbreviated approval after four years of data exclusivity. 21 U.S.C. § 355(j)(5)(F)(ii). In such cases, if the innovator sues for infringement, the data exclusivity period is extended by thirty months (making for a total data exclusivity period that exceeds five years). § 355(j)(5)(F)(ii).

85. *See* Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 150–51 (1989) ("The federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and non-obvious advances in technology and design in return for the exclusive right to practice the invention for a period of years."); AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (describing the "*quid pro quo* of the patent bargain").

86. *Bonito Boats*, 489 U.S. at 151.

withstand a court challenge to limit the free use of valuable, sometimes life-saving medical technology.

Yet, in the context of drug development, many of the requirements of patentability cease to play the same role in ensuring a quid pro quo between the inventor and society. The requirements of the patent system have been tailored to reward and encourage investment in the creation of new ideas. By contrast, much of the investment in pharmaceutical development is directed towards further refinement of existing ideas, in that pharmaceutical companies expend considerable time and resources translating a new idea into a marketable FDA-approved version of the new product.[87] Economists capture this distinction between new ideas and marketable new products by describing two different steps in the innovative process. The term "invention" refers to "the practical implementation of the inventor's idea,"[88] whereas the term "innovation" describes the "functional version of the invention: the version first offered for sale" to consumers.[89]

In the drug context, patents promote both inventive and innovative behavior. Investors will offer to fund research aimed at drug discovery with the expectation that profitable patents will result. The presence or absence of patent protection also plays a role in a firm's decision to invest in clinical development.[90] In the pharmaceutical industry, these later investments that take a drug from the point at which a specific use is discovered through the final stages of clinical trials can equal and even exceed the initial expenditure required in drug discovery.[91]

The innovative function of patent protection has received little attention from patent law. Courts have mainly focused on arguments related to the incentive to invent and disclose.[92] More fundamentally, the requirements of patentability bear little or no relation to whether an idea is worthy of further innovative investment.[93] For example, the

87. This is reflected in the long and costly development period needed to establish safety and efficacy of a promising drug candidate. *See supra* text accompanying notes 59–60 (describing the costs of clinical development).

88. Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation*, 76 CAL. L. REV. 803, 807 (1988) (emphasis omitted).

89. *Id.* (emphasis omitted).

90. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 513 (2009) (noting the pharmaceutical industry's general unwillingness to help fund academic research unless the drug in question is patented).

91. *See supra* note 59 and accompanying text.

92. Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1036–40 (1989) (noting arguments that the profits resulting from a patent monopoly are necessary to encourage investment in bringing inventions to market).

93. *See* STAFF OF SUBCOMM. ON PATS., TRADEMARKS, & COPYRIGHTS OF THE S. COMM. ON THE JUDICIARY, 85TH CONG., AN ECONOMIC REVIEW OF THE PATENT SYSTEM 56 (Comm. Print 1958) (prepared by Fritz Machlup), *available at* http://mises.org/etexts/patentsystem.pdf.

requirements of novelty and non-obviousness are designed to filter out ideas that are already available to society because they are known or easily obtainable by persons skilled in the relevant art. In the context of drug development, a compound that was obvious to create, that has medical uses that were known but never patented, or that had been used for non-medical purposes for years could be ineligible for a patent. Yet, each of these medical innovations would still require expensive, time-consuming, and risky clinical development before they could be approved for use on patients. Also, innovative investment is still necessary where an invention has been protected with patent claims written too narrowly to encompass functionally equivalent products.[94] Such gaps in the patent system can potentially lead investors to discard promising products because the products are not based on patentable ideas.

C. The Costs of Expanded Monopoly Protection

The disjunction between the coverage of the patent system and the need for innovation suggests that some form of supplemental incentive could yield social benefits by increasing innovation in unpatentable products.[95] Yet, any expansion of the monopoly privileges inherent in the patent right also carries potential social costs. The first and most obvious cost associated with monopoly rights is the higher price paid by consumers for patented products.[96] This higher price results in a transfer of wealth from consumers to inventors and innovators.[97] More importantly, a monopoly price can prevent some customers from making a purchase that they would have made at the lower, competitive price. Economists refer abstractly to the loss of such transactions as "deadweight loss."[98] Where the product being priced out of reach is a life-saving or life-changing medicine, this phenomenon can be described more vividly as a tragedy of preventable death and illness.

A second set of costs centers around the way a monopoly-based reward system responds to inputs to the innovative process. This con-

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94. *Cf.* Press Release, Biotech. Indus. Org., *supra* note 23 (claiming that biologics patents are "narrower and easier to 'design around'" than those of small-molecule drugs). It has not been established whether, in the aggregate, biologics patents are more likely to be found invalid or non-infringed than small-molecule patents.

95. The amount of latent innovation potential that exists in unpatentable products is an empirical question subject to debate. *See* Kevin Outterson, *Death from the Public Domain?*, 87 TEXAS L. REV. SEE ALSO 45, 50–52 (2009), http://www.texaslrev.com/seealso/vol/87/responses/outterson.

96. This assumes that the producer of a patented product behaves like a monopolist. *See* RICHARD A. POSNER, ANTITRUST LAW 11–12 (2001).

97. *See id.* at 13.

98. DOMINICK T. ARMENTANO, ANTITRUST AND MONOPOLY 21 (1980) (describing the social welfare losses associated with a restriction of output and price increase due to monopoly power as "deadweight welfare-loss").

cern is closely linked to the first: in order to avoid unnecessary cost to consumers, the monopoly reward should be applied only where it is needed to generate the innovation that made the product available in the first place. The length of the monopoly period is important. If the monopoly period is too long, consumers will effectively pay for drugs that would have been developed with a shorter period. Conversely, if the monopoly period offered is too short to influence investment decisions, developers will receive a windfall, and the public will not benefit from greater innovation encouraged by the monopoly.

A third set of costs relates to the way a monopoly-based reward system values the outputs of the innovative process. A reward system driven by market incentives fails in several ways to encourage behavior that optimizes benefits to public health. Market-driven incentives divert money away from so-called "neglected" diseases, which affect populations that have too few resources to attract investment into new therapies.[99] Research investment may also be inappropriately directed towards duplicative research into "me-too" products that offer little value over existing treatments,[100] or spent on excessive marketing of patented products while failing to provide balanced information to doctors and patients about unpatented alternative treatments.[101]

In particularly egregious cases, a monopoly-based system may reward a producer who has neither invested heavily in new inputs nor produced valuable new outputs. Such a reward was available through an obscure interaction between patent protection and data exclusivity provided by the original Hatch-Waxman Act. The provision provided for a thirty-month stay of generic approval — which amounted to a thirty-month extension of the data exclusivity period — for the resolution of patent disputes.[102] There was no limit on the number of thirty-month stays, meaning innovators could assert a succession of patents on the same product as a strategy for delaying generic competition.[103] While courts eventually found many of these patents invalid or non-

99. *See, e.g.*, Henry Mintzberg, Commentary, *Patent Nonsense: Evidence Tells of an Industry Out of Social Control*, 175 CAN. MED. ASS'N J. 374, 376 (2006), http://www.cmaj.ca/cgi/reprint/175/4/374 (arguing that patents skew research priorities away from investment into diseases occurring predominantly in developing countries); *see also* Pierre Chirac & Els Torreele, *Global Framework on Essential Health R&D*, 367 THE LANCET 1560, 1560 (2006) (detailing the extent to which new medicines targeting diseases that mainly affect people in developing countries have been neglected in terms of new drug research).

100. James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519, 1523 (2007). *But see* Thomas H. Lee, *"Me-Too" Products — Friend or Foe?*, 350 NEW ENG. J. MED. 211, 211 (2004) (defending me-too products on the grounds that they offer marginal improvement in health outcomes and can drive prices down).

101. Mintzberg, *supra* note 99, at 377.

102. *See* 21 U.S.C. § 355(j)(5)(D)(I)(aa)(BB) (2006).

103. Eisenberg, *supra* note 25, at 358.

infringed,[104] delays could be extended for years through the filing of these additional suits.[105] This strategic abuse of the Hatch-Waxman reward system was dubbed product "evergreening," as it allowed companies to maintain monopoly control over existing products without investing in new research and innovation.[106] Fortunately, the statute governing small-molecule approvals was revised in 2003 to correct these abuses, but evergreening behavior may reappear in new contexts, extending monopoly protection without proportionate innovative activity.[107]

The potential for patent evergreening and other strategic gaming must be considered when designing possible reforms. It would be unwise to attempt to close the gaps in the patent system by strengthening or lengthening patent protection, or by discouraging generic firms from challenging weak patents. Such a misguided response would only replace the problem of bad patents for good products with a new problem of good patents for bad products. Instead, effective mechanisms for innovation reform will likely lie outside the patent system.

IV. MECHANISMS FOR REFORM

A. Data Exclusivity as the Favored Candidate for Innovation Reform

Data exclusivity is the most politically popular of several proposed innovation policy incentives where patent protection is unavailable or inadequate to encourage investment in a new drug or biological product. Another option, most thoroughly presented by the patient advocacy group Essential Action, focuses on innovative inputs, using a "cost-sharing" approach through which follow-on firms would be permitted to refer to test data submitted by earlier applicants after compensating those firms for the costs of testing.[108] A comparable cost-sharing approach was previously applied to U.S. approval of

104. Eisenberg, *supra* note 25, at 349.

105. FTC, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION 40 (2002), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (describing cases of additional delays of four to forty months beyond the initial thirty-month period).

106. See Eisenberg, *supra* note 25, at 354.

107. *See id.* at 358 n.54.

108. Fact Sheet, Essential Action, Ensuring Effective Biogenerics Legislation: The Cost-Sharing Approach to Compensation for the Cost of Clinical Trials is Preferable to Data Exclusivity (Jan. 19, 2009), http://www.essentialaction.org/access/uploads/Biogenerics_RD_Cost_Sharing.pdf. The costs of drug development would be assessed according to the actual costs of clinical development, risk-adjusted to account for the likelihood of failure at each stage in the drug development process. Robert Weissman, *Public Health-Friendly Options for Protecting Pharmaceutical Registration Data*, 1 INT'L J. INTELL. PROP. MGMT. 113, 118–19 (2006). Each generic manufacturer would then be required to pay a percentage of those costs according to its share of the market. Weissman, *supra*, at 120.

agricultural chemicals in the 1970s.[109] Several academic commentators have also explored the possibility of large-scale prize funding mechanisms that would focus on innovative outputs, granting prizes to medical innovators in proportion to the overall health benefits achieved by their technology, as opposed to its value in the marketplace.[110] Congress has ignored such mechanisms that attempt to tailor rewards based on cost input or value output, instead favoring a data exclusivity mechanism that relies on protected markets and monopoly pricing to reward innovators.

The success of data exclusivity as a candidate for innovation reform may derive from the established status of monopoly-based incentives as drivers of innovation in the pharmaceutical market. Another reason for the success of this incentive may lie in the broad support it has garnered from the innovator pharmaceutical industry, in particular the Biotechnology Industry Organization ("BIO").[111] BIO spent $7.2 million on lobbying in 2007,[112] the year data exclusivity was first introduced in several proposed follow-on biologics bills.[113]

From a normative standpoint, a carefully calibrated data exclusivity period promises a marginal improvement over patent protection in identifying and rewarding socially beneficial investment. First, the data exclusivity reward would be available to new inventions at the point of regulatory approval, meaning the reward will not depend on the period of time needed for product development or on the strength of the product's patents. Providing exclusivity from the point of approval will offer incentives for developing useful products that have fallen through gaps in the patent system.[114] Second, the reward will be available only when an invention undergoes the costly clinical testing necessary to achieve regulatory approval, making it less likely that

109. 7 U.S.C. § 136a(c)(1)(F)(iii) (2006) (providing for binding arbitration to determine compensation for owner of original data after ten years of data exclusivity).

110. Love & Hubbard, *supra* note 100, at 1520–23; *see also* AIDAN HOLLIS & THOMAS POGGE, INCENTIVES FOR GLOBAL HEALTH, THE HEALTH IMPACT FUND: MAKING MEDICINES ACCESSIBLE FOR ALL 3 (2008), http://www.yale.edu/macmillan/igh/e-library.html.

111. Press Release, Biotech. Indus. Org., *supra* note 23.

112. M. Asif Ismail, *A Record Year for the Pharmaceutical Lobby in '07*, THE CENTER FOR PUBLIC INTEGRITY, June 24, 2008, http://projects.publicintegrity.org/rx/report.aspx?aid=985.

113. Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2(a)(2) (offering up to fifteen years data exclusivity).

114. A right that is triggered so late in the process may also be wasteful to the extent that it allows competitors to invest concurrently in duplicative innovation in a race to the market. *See* Roin, *supra* note 90, at 513–14. Such races, which could occur in secret, would benefit consumers in the short term by introducing two competing products simultaneously, but the risk of such races may also discourage innovators from investing in products that are protected by data exclusivity alone.

innovators will claim the reward without investing in substantial innovative inputs.[115]

While data exclusivity is better at rewarding innovative inputs, it perpetuates some of the costs of the patent system both by allowing innovators to charge monopoly prices to consumers and by failing to reward innovative output according to its value in improving human health. As a market-driven incentive, data exclusivity will continue to encourage investment into me-too products and discourage investment into products targeted at less lucrative diseases.[116] In addition, it will promote aggressive marketing of monopoly-priced products at the expense of more cost-effective alternatives.[117] While the costs of data exclusivity cannot be eliminated without choosing an alternative innovation incentive mechanism, Congress should make efforts to minimize these inherent disadvantages by calculating an appropriate data exclusivity term and limiting opportunities for extension.

B. Appropriate Length of the Data Exclusivity Term

The Hatch and Eshoo proposals being considered by Congress offering twelve or more years of data exclusivity to all biological products do not appropriately reward innovative inputs in the follow-on biologics field. A more appropriate term length would be equal to or less than the five- and three-year periods of data exclusivity offered to small-molecule drugs under existing law.[118] A shorter term would be more fitting because while both biologics and small-molecule drugs require comparable innovative inputs, the technological complexity of biologics renders them less susceptible to competition, and therefore less in need of protection, than their small-molecule counterparts.

The total estimated costs of discovery and development of biologics nearly equal the development costs for small-molecule drugs — approximately $1.24 billion to create a new biologic, compared to

115. This argument rests on the untested empirical assumption that generating the data necessary to achieve regulatory approval for a new product will more closely track with substantial research investment into product development than acquiring a patent. On average, obtaining regulatory approval of a promising drug candidate is quite costly. *See supra* note 59. Yet, an assumption that works on average may not prove valid in individual cases. There may even be entire categories of approvals in which obtaining the approval is relatively inexpensive. For example, gaining approval for a modified version of a product that has already been approved as safe and effective may require less evidence and therefore cost less. *See* Xyntha example *infra* note 142 (noting that the FDA decided to forgo certain steps in the approval process of the drug Xyntha because of its similarity to already-approved ReFacto). If such categories of low-cost approvals can be identified, the data exclusivity reward period offered for those approvals should be reduced to compensate for the diminished need for investment. Unfortunately, the current legislation ignores this point by offering a twelve-year exclusivity period for all new approvals, even those for relatively inexpensive improvements. *See infra* Part IV.C.

116. *See supra* text accompanying notes 99–100.

117. *See supra* text accompanying note 101.

118. 21 U.S.C. § 355(j)(5)(F)(ii)–(iii) (2006).

approximately $1.32 billion to create a new small-molecule drug.[119] Some costs may be higher for biologics, such as the capitalized costs that accrue during biologics' slightly longer clinical development and approval periods (97.7 months as opposed to 90.3 months for small-molecule pharmaceuticals).[120] However, other factors tend to favor reduced costs for biologics, such as the fact that biologics realize a higher probability of clinical success than small-molecule pharmaceuticals (30.2% for biologics as opposed to 21.5% for small-molecule drugs).[121] Biologics and small-molecule drugs therefore have roughly equal development costs.[122]

While innovators in both fields must make comparable investments, follow-on biologics firms will likely face higher barriers to market entry relative to their small-molecule generic counterparts. First, biologics manufacturing is more complex, more variable, and harder to redesign. While it has become possible to safely copy some of the simpler biologics, many of the more complex treatments, such as those used to treat cancer and autoimmune diseases, remain difficult to replicate and characterize.[123] For such products, slight alterations in temperature, timing, or purification conditions can cause clinically significant, yet nearly undetectable, changes in the end product.[124] These issues are exacerbated by the fact that the patent for the drug may only cover early versions of the product produced in the laboratory setting, not the master cell lines and scaled-up industrial process used to produce the product eventually tested on patients and approved by the FDA.[125] Firms can and do seek trade secret protection on these cell lines and processes, forcing follow-on manufacturers to start over after a long and expensive design process.[126]

Second, greater discrepancies between versions of the product would likely call for more testing than is necessary to prove comparability between the follow-on and the innovator for small-molecule drugs, even under the abbreviated approval process.[127] In fact, the

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119. *See* DiMasi & Grabowski, *supra* note 60, at 469.

120. *Id.* at 473.

121. *Id.* at 472.

122. *Id.* at 476.

123. Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 8, 61–62 (2006), http://www.vjolt.net/vol11/issue4/v11i4_a8-Mandel.pdf.

124. *Id.* at 61.

125. Patenting is likely to occur early in the research process. *See supra* text accompanying notes 67–68. The processes and cell lines used to make the product on an industrial scale may not be patented or disclosed. *See* S.D. Roger & D. Goldsmith, *Biosimilars: It's Not as Simple as Cost Alone*, 33 J. CLINICAL PHARMACY & THERAPEUTICS 459, 461 (2008).

126. *See* Roger & Goldsmith, *supra* note 125 ("[T]he master cell lines and details of manufacturing processes involved in producing an originator product are fiercely guarded corporate secrets and are not part of the patent, but are the property of the originator company.").

127. *See* Grabowski et al., *Market for Follow-On Biologics*, *supra* note 13, at 1292–94.

Hatch and Eshoo Amendments would go so far as to require such testing unless an individual determination is made that the tests are unnecessary — a cumbersome obligation not currently required of small-molecule generic drugs.[128] Looking to evidence from Europe, where established comparable abbreviated approval pathways already exist, researchers estimate that each follow-on biologic entry under such a demanding approval pathway will likely involve investments between $100 and $200 million, accompanied by a delay of eight to ten years.[129] In contrast, small-molecule generics approved under the Hatch-Waxman pathway currently cost between $1 and $5 million and take three to five years.[130]

Third, true interchangeability may prove elusive for most follow-on biologics. The legal standard for interchangeability is absolute: at the outset, the risk must be "expected to produce the same clinical result as the reference product in any given patient"; for ongoing treatment, the risk of switching must be no greater than the risk of staying on a given product.[131] This means that even where the overall risk of adverse reaction may be comparable between products, if there is a risk that a given patient may respond well to one product and react poorly to another, the products cannot be approved as interchangeable.[132] While such a strict legal standard may be important to protect patient health where the active ingredient in the follow-on is not exactly identical to the reference product, lack of interchangeability will reduce the extent to which patients may shift between products.[133] As a result, price competition in follow-on products will likely be less intense than price competition in generic drugs.[134]

These barriers to entry and price competition in follow-on biologics suggest that the aggregate effect of competition on innovators will be relatively weak compared to the effect of small-molecule generics. One study estimated that follow-on biologics would initially reduce prices by ten to twenty percent compared to an average seventy-one

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128. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575(a)(2) (2009) (amending 42 U.S.C. § 262(k)(2)(A)(i)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(2)(A)(i)). The follow-on manufacturer may seek a determination from the Secretary to avoid this expense. H.R. 3962 § 2575(a)(2) (amending 42 U.S.C. § 262(k)(3)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(3)).

129. FTC, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION iii (2009), http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.

130. *Id.*

131. H.R. 3962 § 2575(a)(2) (amending 42 U.S.C. § 262(k)(4)(A)–(B)) (emphasis added); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(4)(A)–(B)).

132. This high standard of requiring an identical response from every patient is not required of small-molecule generics, which can be approved for substitution in the pharmacy on a showing that they "can be expected to have the same therapeutic effect as the [reference] drug when administered to patients . . . ." 21 U.S.C. § 355(j)(4)(F) (2006).

133. *See* EMERGING HEALTH CARE ISSUES, *supra* note 129, at 16–17.

134. *See id.*

percent savings resulting from small-molecule generic drugs.[135] While such savings remain valuable,[136] these figures also suggest that biologics require less data exclusivity protection than is currently provided to small-molecule drugs.[137]

It is possible that improvement to the legislation[138] or advances in the science of copying biologics will someday reduce or eliminate these copying costs, increasing the number of follow-on entrants. Yet, it is unlikely that biologics innovators will ever prove more vulnerable to competition than their small-molecule counterparts. For this reason, biologics should not be offered a data exclusivity regime longer than the five- and three- year periods provided to small-molecule drugs under the Hatch-Waxman regime.

C. Limiting Opportunities for Extension

In addition to offering twelve-year terms to new biological products, the Hatch and Eshoo proposals also offer twelve years for modifications and new uses for existing products. Such extensions exacerbate the problem of an already excessive exclusivity period both by allowing for monopoly extensions where innovative inputs are minimal and by skewing investment towards less socially beneficial innovative outputs.

For small-molecule drugs, only new active ingredients are entitled to the full-length five-year data exclusivity period, while clinically significant changes to existing products, such as a new formulation or new use, receive only three years of exclusivity.[139] Under the Hatch and Eshoo Amendments, the twelve-year data exclusivity extension would be available not only to new active ingredients, but also to subsequent applications for products based on the same active ingredient, provided these new applications do not fall within certain poorly-defined exceptions.[140] Subsequent applications that qualify for this

135. Corbitt, *supra* note 21, at 390–91.

136. *See* Press Release, PCMA, *supra* note 11.

137. The FTC has said that existing market barriers would result in sufficient profits for innovators even in the absence of a data exclusivity period. *See* EMERGING HEALTH CARE ISSUES, *supra* note 129, at iii.

138. Sarah Sorscher & Sara Crager, Comment, *Newly Abbreviated Approval Pathway Will Not Solve the Biologics Problem*, HARV. J.L. & TECH. DIG., Mar. 19, 2009, http://jolt.law.harvard.edu/digest/patent/digest-comment-newly-abbreviated-approval-pathway-will-not-solve-the-biologics-problem.

139. *See supra* notes 25, 54.

140. The subsequent applications by the original sponsor or manufacturer do not qualify for twelve years exclusivity if they cover:

> (I) [A] change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or (II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

extension could cover a new use for an existing product, a new slow-release formulation, or a product that has been created using a different purification process.[141]

The additional twelve-year term would be available only for the new, modified version of the product, which means follow-on firms would be free to copy the original variant. Consequently, follow-on firms could seek approval on copies of the original product, assuming the market of customers who will buy copies of the original product is large enough to justify the expenses of copying described in Part IV.B. Yet, there is evidence that by pursuing aggressive marketing strategies with the newer product, the innovator firm will be able to preserve market share by convincing physicians and consumers of the newer product's superiority over the older product.[142] Such marketing would create an evergreening effect that would enable innovators to maintain high profits without sponsoring substantial new innovation.

The twelve-year extensions are problematic for two reasons. First, new formulations and uses for existing products may cost far less to develop than designing entirely new treatments.[143] A twelve-year extension of exclusivity for a small change to an existing product is even

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Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575(a)(2) (2009) (amending 42 U.S.C. § 262(k)(7)(C)(ii)); Hatch Amendment § 602(a)(2) (amending 42 U.S.C. § 262(k)(7)(C)(ii)). The statute does not offer a definition of a "modification to the structure" of a biological product, meaning even slight changes, such as minor differences in amino acid sequence or changes due to post-translational events, may qualify. *Cf.* Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposing modifications to the Public Health Service act, 42 U.S.C. § 252, to exclude changes due solely to post-translational events and minor changes in amino acid sequence from qualifying for the longer term of data exclusivity afforded to entirely new products). The double negatives used in paragraph (I) also create uncertainty as to whether a new "indication" (that is, a new use for) or a new route of administration that involves a structural modification but not a change in safety, purity, or potency would qualify for the twelve-year extension.

141. Paragraph (I) would not exclude new indications along with new formulations, if they relied on a structural change. *See supra* note 140 (describing the vague reach of "modification to the structure" in the statute). A new application for a product that is more "pure" would not fall under the exclusions in paragraphs (I) or (II) and thus qualify for the twelve-year exclusivity period.

142. *See* EUROPEAN COMM'N, PHARMACEUTICAL SECTOR INQUIRY FINAL REPORT 363 (2009) http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf. Wyeth Pharmaceuticals recently employed such a technique to switch customers from ReFacto, a biologic used in treating bleeding episodes in patients with hemophilia, to a newer version of the product, Xyntha, which is made through different manufacturing processes that are still on-patent. *See* Hemophiliavillage, Hemophilia A, ReFacto, http://www.hemophiliavillage.com/refacto.html (last visited Dec. 20, 2009) (describing Xyntha as having the "same molecular structure as ReFacto, with improved purification technology"); *see also* WYETH PHARMACEUTICALS, FULL PRESCRIBING INFORMATION FOR XYNTHA 11 (2008), *available at* https://www.340bpvp.com/public/agreements/suppliers/Protonix.pdf. Xyntha was approved using a new biologics licensing application. *Id.*

143. Xyntha itself was approved after a clinical trial involving fewer than one hundred patients. Biopharma.com, Factor VIII, rDNA, new/Wyeth, http://www.biopharma.com/Samples/154.html (last visited Dec. 20, 2009). The FDA also decided to forgo certain steps in the approval process because of Xyntha's similarity to already-approved ReFacto. *Id.*

less likely to provide a reward proportionate to investment than the initial twelve-year exclusivity period offered for a new product. Second, even though improvements on existing products could carry substantial benefits to consumers by increasing ease of use or lowering the risk of adverse reactions,[144] the health benefits of such tweaks may often be small in scale compared to the benefits of developing previously unknown treatments. The lure of the twelve-year exclusivity term and the potential for extending profits on existing best-sellers is likely to divert research funding away from the expensive process of discovering and developing new, high-impact therapies.

V. CONCLUSION

New legislation allowing for competition in the biologics industry will remain stalled until Congress can come to a compromise on the issue of data exclusivity. The data exclusivity debate highlights gaps in the patent system's effectiveness as a mechanism to encourage development of promising new medical treatments. While data exclusivity is not the only, nor even the most effective, alternative mechanism to patch current gaps in the patent system, it is likely the solution that will allow Congress to move forward with legislation opening a pathway for follow-on biologics. Data exclusivity is better than patent protection at rewarding new pharmaceutical innovation because data exclusivity is only granted to innovators who make the investments necessary to complete a costly regulatory approval process. Yet, it is highly unlikely that biologics, as a class, will require the twelve-year reward period currently being considered by Congress as part of healthcare reform. Rather than offer an appropriate reward for investment, the Hatch and Eshoo Amendments provide excessive protection for new products and encourage strategic behavior by innovators. These features make the legislation poorly tailored to serve as a mechanism for innovation policy reform.

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144. For example, the traditional formulation of Amphotericin B, a drug useful in treating systemic fungal infections, required multiple injections and was highly toxic. Kishor M. Wasan et al., *The Global Access Initiative at the University of British Columbia (UBC): Availability of UBC Discoveries and Technologies to the Developing World*, 98 J. PHARMACEUTICAL SCI. 791, 793 (2009). Development of a lipid-based Amphotericin B formulation for oral administration promises lower toxicity and greater ease of use, making it a promising candidate for treatment of visceral leishmaniasis, a disease that affects over 200 million people, mostly in developing countries. *Id.* New uses for existing products may have health benefits that dwarf the benefits of the original use. *See, e.g.*, FRAN HAWTHORNE, INSIDE THE FDA 109–15 (2005) (describing the success of Thalidomide at treating leprosy). However, the twelve-year extensions are likely to prove ineffective at encouraging the development of new uses, as physicians are free to prescribe existing products off-label. *See* Eisenberg, *supra* note 25, at 359–60.