MISPLACED FEARS IN THE LEGISLATIVE BATTLE OVER AFFORDABLE BIOTECH DRUGS

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ABSTRACT

Much like tort reform, the debate over recently enacted legislation on biotech drugs—and particularly regulatory supplements to patent protection—has taken on a significance that dwarfs its impact on prescription drug expenditures. Under the Health Care Reform legislation, Congress enacted two major reforms: First, creation of an abbreviated Food and Drug Administration (FDA) approval process for follow-on biologics (FOBs), which are the analogues of generics for biotech drugs. Second, establishment of a twelve-year "data exclusivity" period in which clinical testing data collected by brand-name innovators can not be used by producers of FOBs to satisfy FDA testing requirements. While the abbreviated FDA approval process enjoys broad support, the data-exclusivity provision has been hotly contested, including strong opposition from the Federal Trade Commission.

We argue that the debate over the duration of regulatory data exclusivity is a sideshow. Current estimates suggest that the differences in duration of the data exclusivity period that were debated, essentially between seven and twelve years, would not materially affect aggregate expenditures on prescription drugs. For this and other reasons, any potential benefit to patients that might result from a shorter period of data exclusivity are likely to be outweighed by the financial risks to the biotech industry, and particularly the negative effects on investments in research and development.

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More importantly, we believe that the focus on data exclusivity has obscured a critical flaw in the new law. Policymakers ignored the weak competition in markets for biotech drugs, which will erase much of the cost savings predicted from experience with generic versions of conventional drugs under the Hatch-Waxman Amendments to the Food, Drug and Cosmetics Act. This difference implies that the benefits of having an abbreviated FDA approval process will not be realized until policies exist that overcome the significant barriers to market entry for manufacturers of follow-on biologics—without effective competition, the pricing of biotech drugs could remain high indefinitely. We close the article by suggesting several policies to address this gap in the Health Care Reform legislation.

I. INTRODUCTION

Much like tort reform, the debate over the provisions in the new Health Care Reform law that revise the regulation of biotech drugs—and particularly regulatory supplements to patent protection—took on a significance that dwarfed their projected impact on prescription drug expenditures. This article examines the legal, economic, and policy dimensions of this debate. We argue that the controversy over regulatory "data exclusivity" was a sideshow and that the cost-saving benefits of the new law will not be realized until policies are enacted that overcome the systemic barriers to competition in the markets for biotech drugs.[1]

Biotech drugs are the fastest growing and most costly class of prescription drugs.[2] Moreover, despite estimates that biotech drugs are used to treat just three percent of the global population, it was estimated that in 2008 they accounted for forty-four percent of the global profits from prescription drugs.[3] In the United States, biotech drugs generate $50 billion annually, making them

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1 The term "biotech drug" refers to drugs produced in living cells, most of which are recombinant proteins. Insulin was the first biotech drug to be commercialized and was quickly followed by others that substituted for natural proteins (e.g., human growth factor). Gary Pisano, SCIENCE BUSINESS: THE PROMISE, THE REALITY, AND THE FUTURE OF BIOTECH 27 (2006).

2 LESLIE TUCKER, NAT'L HEALTH POLICY FORUM, PHARMACOGENOMICS: A PRIMER FOR POLICYMAKERS 11 (2008), http://www.nhpf.org/library/background-papers/BP_Pharmacogenomics_01-28-08.pdf; *see also* Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479, 479 (2008).

3 PRICEWATERHOUSECOOPERS, PHARMA 2020: MARKETING THE FUTURE—WHICH PATH WILL YOU TAKE? 13–14 (2009), http://www.pwc.com/en_GR/gr/surveys/assets/pharma-2020-marketing-future.pdf.

significant in absolute terms to the biotech industry.[4] Further, with the growing number of biologics approved by the Food and Drug Administration (FDA), expanding conditions that biologics treat, and high profit margins that they command, there is every reason to believe that the market share of biologics will continue to grow.[5]

These trends fueled congressional interest in legislation creating an abbreviated FDA approval process for so called "follow-on biologics" (FOBs), which are the analog of generics for biotech drugs. Legal gaps and technical differences necessitated creation of a separate FDA review process for FOBs. Legally, most biotech drugs are regulated under the Public Health Services Act and are thus not eligible for the abbreviated approval process created under the Hatch-Waxman Amendments[6] to the Food Drug & Cosmetic Act (FDCA).[7]

Technically, the chemical structures of biotech drugs are much more complex than conventional drugs, which raises distinct challenges for assessing the safety and potency of an FOB relative to the name-brand drug on which it is based. Subtitle A under Title VII of the Health Care Reform law, "Biologics Price Competition and Innovation Act of 2009" (BPCI),[8] reflects these differ-

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4 John E. Calfee, *Facing Reality on Follow-On Biologics*, HEALTH POL'Y OUTLOOK (Am. Enter. Inst. for Pub. Policy Research, Washington, D.C.), Apr. 2007, at 1, *available at* http://www.aei.org/docLib/20070423_200704AHPOg.pdf.

5 Michael Lanthier et al., *Economic Issues with Follow-On Protein Products*, 7 NATURE REV. DRUG DISCOVERY 733, 733–34 (2008); *see also* John E. Calfee & Elizabeth DuPre, *The Emerging Market Dynamics of Targeted Therapeutics*, 25 HEALTH AFF. 1302, 1304 (2006), *available at* http://www.aei.org/docLib/20060912_EmergingMarketDynamics.pdf (noting biologics resistance to pricing pressures).

6 Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified in 15 U.S.C. §§ 68b, 68c, 70b; 21 U.S.C. §§ 301, 355, 360cc; 28 U.S.C. § 2201; 35 U.S.C. §§ 156, 271, 282) (hereinafter "Hatch-Waxman Amendments").

7 Act of July 1, 1902, ch. 1378, Pub. L. No. 57-244, 32 Stat. 728 (1902); FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 3 (2009), http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf (hereinafter "FTC"). For historical reasons, a few biotech drugs are regulated under the FDCA, including insulin and human growth hormone. Legally, these biotech drugs are amenable to abbreviated approval processes under the FDCA, but FDA has never approved a true generic version of any of these drugs, due in large part to their chemical complexity. FDA has approved follow-on versions of some biotech drugs regulated under the FDCA, including most notably Omnitrope, a follow-on version of recombinant human growth hormone. *See* Press Release, Sandoz, Sandoz receives FDA approval for Omnitrope® Pen 10 with liquid cartridge (Sep. 3, 2008), http://www.lek.si/eng/media-room/press-releases/3948/.

8 Patient Protection and Affordable Care Act, Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, Title VII, Subtitle A, §§ 7001–7003 (2010); *see also* Christopher M. Holman, *A Response to the FTC's Report on Follow-On Biologics* 2 (October 1,

ences insofar as it provides for enhanced FDA review relative to that of conventional drugs under the Hatch-Waxman Amendments, while still seeking to reduce the costs of and time required for approving FOBs.

Proponents of the BPCI subtitle claimed that it would promote competition and lower prices in the market for biologic drugs, which can be stratospherically high—costs in some cases exceed $100,000 for a treatment regimen.[9] Like the Hatch-Waxman Amendments, a key feature of the BPCI subtitle is a provision that will allow an FOB applicant to rely on data generated by the original drug maker to secure FDA marketing approval.[10] By reducing the time for and costs of obtaining FDA approval, this provision will facilitate market entry of FOBs. Yet insofar as the policy succeeds, it will also erode the profits of the original drug producer and the market incentives for developing new drug products.[11]

Broad support has existed for creation of an abbreviated pathway for FOBs. The biotech industry's support, however, was contingent on the availability of patent protection, or a regulatory variant of it, that would ensure a return on investment sufficient to justify the high costs and substantial risks associated with bringing a biotech drug to market. Investments in the biotech and pharmaceutical sectors are massive—estimates suggest that average costs of commercializing a biotech drug exceed $1 billion, with a large fraction of them attributable to capital costs that must be borne for development periods that average twelve years.[12] As these qualifications suggest, the controversy over the

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2009), *available at* http://ssrn.com/abstract=1481350 (summarizing the provisions of the Health Care Reform legislation).

9 Pedro Cuatrecasas, *Drug Discovery in Jeopardy*, 116 J. CLINICAL INVESTIGATION 2837, 2840 (2006), *available at* http://www.jci.org/articles/view/29999/pdf (describing biotech drugs with costs from about $110,000 per year to more than $200,000 per year).

10 Biologics Price Competition and Innovation Act, Pub. L. 111-148, § 7002.

11 David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20 HEALTH AFFAIRS 11, 12 (2001), *available at* http://www.laskerfoundation.org/advocacy/pdf/cutler_mcclellan_2001.pdf; Richard G. Frank & Joseph P. Newhouse, *Should Drug Prices Be Negotiated Under part D of Medicare? And If So, How?*, 27 HEALTH AFFAIRS 33, 39 (2008).

12 Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 475–76 (2007), *available at* http://www.manhattan-institute.org/projectfda/wiley_interscience_cost_of_biopharm.pdf. For pharmaceuticals generally, *see* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180–81 (2003), *available at* http://www.gmp.asso.fr/Documents/Biblio/Cost%20of%20drug%20Developement.pdf; Christopher P. Adams & Van V. Brantner, *Estimating The Cost of New Drug Development: Is It Really $802 Million?*, 25 HEALTH AFFAIRS 420, 422–24 (2006), *available at* http://content.healthaffairs.org/cgi/reprint/25/2/420.

BPCI subtitle centered on differing views about the appropriate balance between assuring adequate market returns to sustain innovation and minimizing the costs of biotech drugs to ensure patient access.

One of the most contentious provisions in the BPCI subtitle grants an innovating company a twelve-year period of "data exclusivity" to supplement traditional patent protection, with the terms running concurrently.[13] This measure works in conjunction with the abbreviated review process for FOBs, which as outlined above allows FOB producers to rely on data generated by the innovator company to obtain FDA marketing approval. Beginning on the date that a drug is approved for marketing, data exclusivity precludes FOB producers from relying on the innovator's data to obtain FDA approval of an FOB prior to the expiration of the twelve-year data exclusivity period.[14]

Importantly, data exclusivity neither creates restrictions on the use of the drug itself, nor does it preclude FOB makers from conducting their own studies to obtain FDA approval. Data exclusivity instead operates as a backup to patents on a drug by maintaining, for a limited period of time, the high barrier to market entry associated with the stringent FDA requirements for clinical testing data on a new drug. It also has clear precedent. The Hatch-Waxman Amendments provide up to five years of data exclusivity for conventional drugs,[15] although this shorter period often lapses long before patent protection expires.

The need for twelve years of data exclusivity is driven by concerns that patent protection is less effective for biotech drugs than it is for conventional drugs. Further, whereas the Hatch-Waxman Amendments require the active ingredients in generic and brand-name drugs to be identical,[16] the BPCI subtitle affords FOB producers leeway to modify production processes and the chemical structure of biologics themselves.[17] The FOB provisions in the new law create an abbreviated pathway for "biosimilar" variants of a brand-name drug—chemical identity is not required. This added flexibility enhances the potential for FOB producers to design around patents on a brand-name drug while still retaining sufficient biosimilarity to take advantage of FDA's abbreviated approval process. The complexity of biotech drugs exacerbates these problems by affording competitors many degrees of freedom to design around patent claims.

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13 Pub. L. 111-148, § 7002(a)(7).

14 *Id.*

15 21 U.S.C. § 355(c).

16 21 U.S.C. § 355(j).

17 Holman, *supra* note 8, at 9.

Critics of data exclusivity assert that little concrete evidence exists to substantiate fears about the adequacy of patent protection and that, in any event, other barriers to entry will mitigate such deficiencies.[18] They point to studies finding that the heightened FDA review required for FOBs and high costs of manufacturing biotech drugs will limit market entry by FOB producers. For biotech drugs with mid-sized markets, economists estimate that the number of entrants will on average be three, as opposed to the average of nine generic producers for conventional drugs, and that prices will drop only 10–30 percent once FOBs are marketed.[19]

The biotech industry counters that the heightened market barriers to FOBs do not eliminate the need for data exclusivity to supplement patent protection. In fact, the economic studies used by critics of supplemental patent protection conclude that a twelve-year period of data exclusivity is essential to the profitability of biotech drugs.[20] Biotech representatives argue that, contrary to critics' claims, economic projections find that FOB market barriers alone will not sustain the price premiums necessitated by the large upfront costs of drug development. Furthermore, if patent protection proves to be effective, in most cases the data exclusivity period and corresponding patent terms will run out at roughly the same time,[21] implying that data exclusivity will rarely extend the market exclusivity of a drug maker.[22] Data exclusivity may also encourage development of clinically important biologics that would otherwise be abandoned because robust patents on the active ingredient are unavailable.[23]

Prevailing uncertainties provide grounds for and against the longer twelve-year term of data exclusivity for biotech drugs. What is unequivocal, though, is that the effects either way on prescription drug expenditures will be

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18 FTC, *supra* note 7, at iii–viii.

19 Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 446, 447 (2007), *available at* http://fds.duke.edu/db?attachment-25--1301-view-323.

20 Grabowski, *supra* note 2, at 479; *cf.* Alex M. Brill, *Proper Duration of Data Exclusivity for Generic Biologics: A Critique* (November 2008), *available at* http://www.tevadc.com/Brill_Exclusivity_in_Biogenerics.pdf (arguing that seven years of data exclusivity would provide sufficient incentives).

21 A recent study showed that conventional small molecule drugs average of 11 to 13 years of de facto exclusivity prior to generic competition, primarily as a result of patent protection that extends beyond the short data exclusivity period provided under Hatch-Waxman. FTC, *supra* note 7, at 43 (citing Henry G. Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 28 MANAGERIAL & DECISION ECON. 491, 493 (2007)).

22 Holman, *supra* note 8, at 6.

23 *Id*. at 7.

modest. According to a 2007 estimate by the Congressional Budget Office, establishing an abbreviated FDA approval process for FOBs will reduce national spending on prescription drugs by just 0.5 percent over the first ten years of the program.[24] The impact of a shortened data exclusivity period would be a fraction of this estimate, since the debate was over seven versus twelve years as opposed to the "indefinite" status quo. It will have a much smaller effect on overall health care costs, as drugs account for only about ten percent of total health care expenditures in the United States.[25]

We will argue that, on balance, the potential benefit to patients that might have resulted from a shorter period of data exclusivity for innovators is outweighed by the financial risks to the biotech industry, and particularly the negative impacts on investments in research and development.[26]

More importantly, we believe that the focus on data exclusivity has obscured a critical flaw in the new law. Policymakers ignored the weak competition in markets for biotech drugs, which will erase much of the cost savings predicted from experience with generic versions of conventional drugs under the Hatch-Waxman Amendments to the FDCA. This difference implies that the benefits of having an abbreviated FDA approval process will not be realized until policies exist that overcome the significant barriers to market entry that remain for manufacturers of follow-on biologics—without effective competition, the pricing of biotech drugs could remain high indefinitely. After examining the arguments for and against data exclusivity and discussing the specific barriers to market entry of FOBs, we close the Article by proposing several policies to address this gap in the Health Care Reform legislation.

II. LIMITATIONS OF THE PATENT SYSTEM FOR BIOLOGICS

The limitations of patent protection for biotech drugs is perhaps best understood by analogy. The scope of a patent is determined by its claims, which are based on a set of defining limitations or "elements"— roughly speaking, the greater the number of elements, the more conditions must be met for an accused invention to infringe a patent claim and the narrower its scope. If the patent claim on a chair had only two elements, say a horizontal seat and at least

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[24] CONG. BUDGET OFFICE, COST ESTIMATE FOR S. 1695: BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2007, at 1 (2008), http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf; *see also* Lanthier, *supra* note 5, at 736.

[25] David M. Cutler, *The Demise of the Blockbuster?*, 356 NEW ENG. J. MED. 1292, 1293 (2007).

[26] Data exclusivity also ensures parity with traditional drugs, which benefit from patent terms that are comparable to the twelve-year term being proposed. Grabowski & Kyle, *supra* note 21, at 493.

three legs, many types of chairs would infringe the patent. Conversely, if the claim on a chair had twenty defining elements, each of which must be found in a competing chair, far fewer chairs would infringe it.

The complexity of biotech drugs frustrates standard approaches to drafting patent claims.[27] While traditional small-molecule drugs have dozens of atoms, biotech drugs are typically 1000-fold larger, and have multiple levels of structural organization that are essential to their functionality.[28] At the same time, scientific understanding of the relationship between structure and function in a biotech drug is still only partially understood.[29] As a consequence, scientists are unable to predict whether even modest variations in the molecular sequence of a biotech drug will alter its functionality, or change it from an efficacious treatment to a form that is potentially lethal. Similarly, even slight modifications in a production process can adversely affect cellular biochemical processes that are essential to the activity of a protein, leading to changes in safety or potency.[30]

This complexity creates two mutually reinforcing problems for innovators. The size and complexity of biotech drugs affords competitors many molecular degrees of freedom, which provide numerous opportunities to design around an original innovator's patents. Additionally, the scientific uncertainties surrounding the relationship between changes in structure and protein function bounds the original inventors' capacity to draft and support broad patent claims.

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27 Pamela Jones Harbour, FTC Commissioner, The Competitive Implications of Generic Biologics, Remarks at the Meeting of the ABA Sections of Antitrust and Intellectual Property Law 14 (Jun. 14, 2007) (transcript *available at* http://www.ftc.gov/speeches/harbour/070614genbio.pdf) (suggesting that "for many biologics, patents may not be an obstacle to generic entry"); Rebecca S. Eisenberg, *The Shape of Things to Come: Pharma's Nonobviousness Problem*, 12 LEWIS & CLARK L. REV. 375, 376–78 (2008); Editorial, *Risks, Returns and Reassurance*, 7 NATURE REV. DRUG DISCOVERY 545, 545 (2008) (suggesting "that the patents for biologics could be considerably more vulnerable to challenges or circumvention" than patents on traditional drugs).

28 CONG. RESEARCH SERV., RL33901, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 2 (2008), *available at* http://assets.opencrs.com/rpts/RL33901_20090803.pdf; Martin Kuhlmann & Adrian Covic, *The Protein Science of Biosimilars*, 21 [Supp. 5] NEPHROLOGY DIALYSIS TRANSPLANTATION v4 (2006), *available at* http://ndt.oxfordjournals.org/cgi/reprint/21/suppl_5/v4. Design-around competition is also potentially easier for biologics, as once a given pathway is identified, competitors can select other targets associated with it. Grabowski, *supra* note 2, at 484; Calfee & DuPre, *supra* note 5, at 1306.

29 David M. Dudzinski et al., *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 NEW ENG. J. MED. 843, 847 (2008).

30 Kuhlmann & Covic, *supra* note 28.

If we return to the chair example, to the extent that the basic structure and engineering of a chair is fixed and simple, patentees will be able to draft robust patent claims and competitors will have limited prospects for designing around them. On the other hand if a chair has 1000 parts, each of which may or may not be essential to its operation, it would afford many opportunities for competitors to construct modest variations that, due to its complexity, the inventor would neither be able to anticipate nor to encompass by a broad but legally supported claim. Further, from a purely practical perspective, it would be impossible for the inventor to analyze all of the potential variations on the invention.

The erratic evolution of patentability doctrines, particularly as they apply to biotech drugs, reflects these inherent tensions. The size and complexity of biotech drugs have led the Court of Appeals for the Federal Circuit and the Patent and Trademark Office (PTO) to evaluate the patentability of biotech inventions using varying degrees of stringency. However, even absent a heightened standard for obtaining broad patent claims, biotech drugs are uniquely vulnerable to design-around strategies. Litigation trends bear out this doctrinal instability and reveal that enforcement of biotech patents is less certain, and generally less successful, than it is for conventional drugs.

A. The Limited Success of Infringement Suits Involving Patents on Biotech Drugs

The most important patents on traditional drugs are those that cover the active compound in a drug formulation. Such "composition of matter" patents are valuable because they cover any manufacture, use, or sale of the active ingredient in a drug, regardless of the process used to make it, the formulation of a drug product, or the medical condition treated. Importantly, these patents cover improved formulations of a drug and new methods of use developed after the original patent filing.

Most drug companies will not risk the large upfront investments required to develop a drug if the active compound itself cannot be patented. Recent data on litigation involving the enforcement of drug patents illustrates the power of composition-of-matter patents. In a study conducted by Bernstein Global Wealth Management (the "Bernstein Report"), the researchers found that out of 14 total patent challenges involving composition-of-matter claims, nine were won by the branded drug, three settled, and the generic challenger won

only twice.[31] The results invert for the 23 patent litigation cases involving other types of patents (e.g., certain types of formulations and combination products); the brand-name company never prevailed in court, while the generic challenger won 13 of the cases, and 10 cases settled out of court.[32]

These results, while based on a modest number of cases, reflect trends that date back to the first generation of biotech drugs discovered (e.g., insulin).[33] In the early cases, patents covering processes and reagents used in drug production played the primary role, rather than composition-of-matter patents claiming the active ingredient. In many cases, competitors were able to bring a variant of an innovator's biotech drug to market while avoiding patent infringement by making modest modifications to the production of the drug and the drug itself.[34]

This basic scenario continues to stoke fears about the recently enacted BCPI subtitle. Industry concern was heightened by provisions in the law that allow FOB producers to use an abbreviated FDA approval process—which is premised on using innovator-generated data to avoid the high costs of clinical testing—when their compounds contain substantial, and largely ill-defined, structural difference from the original drug.

An abbreviated FDA approval process could permit FOB producers to have their cake and eat it. They could benefit not only from the research conducted by the original innovator but also from its clinical data to gain rapid, low-cost FDA approval—and all while circumventing the patent on the active ingredient. The frequency with which this may occur will depend on FDA's standard for "biosimilarity," as this will determine the degree of structural variation permitted and hence the latitude FOB makers will have to circumvent innovator patents, while still benefiting from the innovator's clinical testing data.[35]

The history of cases involving enforcement of composition-of-matter patents on biotech drugs has elevated innovators' fears. There does not appear to be a single appellate-level decision in which a patent on the active ingredient

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31 BERNSTEINRESEARCH, PARAGRAPH IV LITIGATION: A GUIDE FOR THE PERPLEXED 6 (Oct. 2007) (on file with author).

32 *Id*.

33 Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555 (Fed. Cir. 1997); Hormone Research Found., Inc. v. Genentech, Inc., 904 F.2d 1558 (Fed. Cir. 1990).

34 Christopher M. Holman, *Learning from Litigation: What Can Lawsuits Teach Us About the Role of Human Gene Patents in Research and Innovation?*, 18 KAN. J.L. & PUB. POL'Y 215, 223–29 (2009).

35 Under the proposed FOB legislation, reliance on innovator data will only be available to an FOB that is "biosimilar" to the innovator biologic; it remains unclear how stringently FDA will define biosimilarity. Holman, *supra* note 8, at 9 n.28.

of a biotech drug has been found valid and infringed.[36] At the district court level, infringement of a valid composition-of-matter patent has been found twice,[37] but both are recent decisions involving a family of related patents claiming variations of Amgen's blockbuster drug erythropoietin.[38] Even these successes, however, must be qualified. In *Amgen v. HMR*, the asserted patent was found to be valid and infringed by the district court only after multiple appeals, and the district court decision has not been appealed.[39] Similarly, the district court's decision on patent validity in *Amgen v. Hoffman-La Roche* was recently vacated and remanded for reconsideration.[40] In response, Amgen and Hoffman-La Roche settled their dispute, so no appellate decision will be forthcoming in this case either.[41]

While composition-of-matter patents have often proven ineffective in protecting biotech drugs, patentees have had somewhat more success asserting patents that cover genes, genetic constructs, and recombinant cells used in the production of a biotech drug, as well as the production processes themselves.[42] Amgen's successful enforcement of patents covering genes and production methods used to produce erythropoietin has been notable in this respect,[43] but numerous examples exist in which competitors have successfully designed around such patents and avoided infringement liability.[44] Even critics of using data exclusivity to augment patent protection acknowledge this vulnerability to simple design-around strategies.[45]

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36 The U.S. Court of Appeals for the Federal Circuit has found composition-of-matter patents claiming a biologic active ingredient not infringed by a competing product. *See, e.g.*, Amgen Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1316 (Fed. Cir. 2006) (U.S. Patent No. 5,621,080, claiming recombinant erythropoietin, not infringed by competing recombinant erythropoietin product); *Wellcome Found.*, 29 F.3d 1555, 1567 (Fed. Cir. 1994) (U.S. Patent No. 4,752,603, claiming tissue plasminogen activator, not infringed by biologic employing structurally modified form of the protein).

37 Amgen, Inc. v. F. Hoffman-La Roche Ltd., 581 F. Supp. 2d 160 (D. Mass. 2008); Amgen Inc. v. Hoechst Marion Roussel, Inc., 579 F. Supp. 2d 199 (D. Mass. 2008).

38 Holman, *supra* note 8, at 9–10.

39 Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. REV. 295, 329–30 (2007).

40 Amgen Inc. v. F. Hoffman-La Roche Ltd., 580 F.3d 1340 (Fed. Cir. 2009) (the district court's judgment that the COM claims were infringed was affirmed).

41 Amgen v. F. Hoffman-La Roche Ltd., Doc. No. 05-12237, Document 1775, Stipulation and Order (Dec. 22, 2009).

42 Holman, *supra* note 39, at 295.

43 *Id*. at 295, 329–30.

44 Holman, *supra* note 34, at 215, 223–29.

45 FTC, *supra* note 7, at 45.

Patents on technologies used in the production of biotech drugs are subject to an alternative, potentially more troubling form of circumvention. A competitor who produces a biotech drug outside of the U.S. in a jurisdiction in which the innovator has not patented its production technologies, or where enforcement is difficult, may avoid the patent altogether.[46] This could be a particularly significant issue if FOB production shifts to rapidly developing countries, such as China, where patent protection remains weak and uneven.

B. Legal and Technical Limits on the Scope of Biotech Patents

Conventional wisdom for many years held that stringent, biotechnology-specific standards of patentability severely limited the scope of patent protection available for biotech drugs.[47] In 2007, one of us conducted a comprehensive survey of court cases and patent office decisions involving the written description requirement for patentability of biotechnology inventions (hereinafter the "Holman Study").[48] The study did not find evidence of a heightened written description requirement for biotech drugs. To the contrary, the Holman Study discovered many instances in which patentees overcame challenges to broad patent claims encompassing numerous variants of basic gene or protein structures.[49]

These findings have been misinterpreted by critics of data exclusivity. Critics make the erroneous inference that because biotech drugs are not subject to heightened patentability standards, the scope of their protection is not materially different from that of traditional small-molecule drugs, or alternatively that accepted claiming strategies exist that can ensure adequate patent coverage.[50]

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46 Holman, *Learning from Litigation*, *supra* note 34, at 229–31.

47 Christopher M. Holman, *Is* Lilly *Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of* Eli Lilly *and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1 (2007) (collecting law review articles and judicial decisions expressing view that written description requirement substantially limits effective scope of patent protection available for biotechnology inventions).

48 *Id.*

49 *Id*. at 78– 82 (concluding that (1) the written description requirement was not generally functioning as a super-enablement standard; (2) neither the courts nor the PTO had formulated a coherent interpretation of written description for biotech drugs that went beyond the enablement requirement; and (3) the written description requirement was not narrowly restricting the scope of patent claims on biotech drugs).

50 FTC, *supra* note 7, at iii–viii, 36–37.

The Holman Study identified a number of judicial decisions in which a patent claiming a biotechnology-based invention was found to satisfy the written description requirement, but only one, *Regents of the University of California v. Eli Lilly & Co.*,[51] involved a biotech drug. Furthermore, *Eli Lilly* did not involve a composition of matter patent claiming the active ingredient, in this case insulin, but rather a patent on the corresponding gene for insulin, as well as claims on recombinant host cells and other compounds used to produce it. In the only other case involving a biotech drug, *Amgen v. HMR* (discussed above), the court sided with the patent owner in rejecting the patentability challenge raised by the alleged infringer, but this challenge also involved claims on recombinant cells used to produce the biotech drug, as opposed to the active compound itself.

The availability of "percent identity claims," and their analogues, for biotech drugs is a claiming strategy often cited by critics to argue that biotech patents provide adequate protection. A percent-identity claim allows the patentee to obtain rights over structural variants of a biotech drug, such as where a patent claim covers any protein with an amino acid sequence that retains the functionality of a reference protein (i.e., the active ingredient of a biotech drug) and shares some defined degree of percent structural identity with it (typically 90% or higher).[52]

Some commentators have concluded that the large breadth afforded by such claims—which literally cover millions of structural variants of a biotech drug—negates concerns about the adequacy of biotech patents.[53] This inference runs into two countervailing facts. First, not a single example exists of a percent-identity claim on a biotech drug being successfully enforced against a biologic competitor. The jury is therefore out on whether percent-identity claims in practice provide effective protection for biotech drugs.

Second, recent legal developments cut against the viability of broad percent-identity claims. In 2008, the PTO issued revised written description guidelines that, in significant respects, reverses the relatively lenient PTO guidelines on written description that had been in effect since 1999.[54] The revised guidelines strengthen the written description requirement for biotechnology

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51 119 F.3d 1559 (Fed. Cir. 1997).

52 A standard example is the following: "a protein [the biotech drug in this case] comprising an amino acid sequence sharing at least 90 percent identity with amino acid sequence" disclosed in the patent.

53 FTC, *supra* note 7, at 36–37.

54 PTO, Written Description Training Materials (March 2008), *available at* http://www.uspto.gov/web/menu/written.pdf.

inventions, making it distinct from and more restrictive than the enablement requirement for patentability.[55] Moreover, because of the underlying unpredictability of structure-function relationships for biotech drugs, the revised guidelines are likely to narrowly circumscribe the scope of percent-identity claims that can meet the PTO's revised standard for written description. Bearing out this change in PTO policy, anecdotal accounts suggest that the PTO is already applying the written description requirement as a "super enablement" standard for claims on biotech drugs, effectively foreclosing broad percent-identity claims.[56]

The recent BPAI decision in *Ex parte Kubin* is representative of the shifting doctrines relevant to the scope of patent claims on biotech patents.[57] In this case, the BPAI affirmed a PTO examiner's rejection of claims covering all DNA molecules that encode proteins that retain its function and share 80 percent, or more, identity with the protein disclosed in the patent claim. The BPAI found that, although the applicant had enabled the genus of molecules encompassed by the claim, the patent failed the written description requirement because it did not identify which molecules sharing 80 percent or greater sequence identity retained the function of the original protein. This case marks a sharp departure from earlier BPAI decisions, which had been far less strict in this respect, and signals that under the revised PTO guidelines biotech drugs are likely to be given substantially narrower patent protection than they had prior to 2008.

The trend under the PTO guidelines towards heightened patentability standards for biotech drugs was recently reinforced by the Federal Circuit in *Ariad v. Eli Lilly*.[58] The en banc court affirmed the continuing vitality of the written description requirement as a doctrinal tool for limiting the scope of biotechnology patents.[59] Further, the Federal Circuit has placed a renewed emphasis on the enablement requirement that reinvigorates its function as a primary doctrinal limit on patent scope.[60] The precise contours of the enablement and

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55 Holman's Biotech IP Blog, PTO Issues Revised Written Description Guidelines, Further Muddying the Waters, *available at* http://holmansbiotechipblog.blogspot.com/2008/04/pto-issues-revised-written-description.html (Apr. 24, 2008, 16:01 CST).

56 Based on conversations with patent attorneys working in this area.

57 83 U.S.P.Q. 2d (BNA) 1410, 2007 WL 2070495 (B.P.A.I. 2007).

58 Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010).

59 *Id.* at 1351–52.

60 *See, e.g.*, Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274 (Fed. Cir. 2007); Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007); Halliburton Energy Services, Inc. v. M-I LLC, 514 F.3d 1244 (Fed. Cir. 2008); Sitrick v. Dreamworks, LLC, 516 F.3d 993 (Fed. Cir. 2008).

written description requirement remain poorly defined, but in tandem they have the potential—as the Federal Circuit explicitly acknowledges in *Ariad v. Eli Lilly*—to substantially limit the scope of patent protection available for biotech drugs.[61]

The changing status of a heightened patentability standard does not negate either the weak empirical record of patent enforcement for biotech drugs or the inherent limits of patents on them. While heightened patentability standards exacerbate the limitations of composition-of-matter patents on biotech drugs, even patents with broad claims will be relatively easier to circumvent because of the huge number of structural variants that exist for biotech drugs. This point is of particular importance for the BCPI subtitle, which opens the door to potentially broad structural variation for regulatory purposes. In particular, patents that in absolute terms cover numerous structural variants will nevertheless be ineffective in blocking competitors if they do not encompass the range of structures allowable under the weaker "biosimilarity" standard that FDA will be implementing under the BCPI subtitle.

III. CHARACTERISTICS OF BIOTECH DRUGS THAT IMPEDE COMPETITION

The distinctive characteristics of biotech drugs—their size and complexity—that undermine patent protection also place greater demands on the FDA approval process and increase the technical challenges of manufacturing them. The added costs that result increase the barriers to market entry for FOB manufacturers. By contrast, FDA review of generic versions of conventional drugs is straightforward and drug manufacturing processes are simple and extremely cheap.

Economists project that these barriers will reduce the average number of FOB producers for biotech drugs, lower competition, and limit the drop in prices that can be expected once FOB manufacturers enter a market. Competition will be complicated further because FOBs are not expected to be precisely interchangeable with their brand-name counterparts. In short, absent other policies the new abbreviated FDA approval process for FOBs will not come close to

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[61] *Ariad*, 2010 U.S. App. LEXIS 5966, at *45–46 [opinion pp. 26–27] (stating that the written description requirement has never operated as a "super enablement" standard, but then going on to recognize that the unpredictability of the relationship between the structure and function of biomolecules there is often a significant difference between "describing an invention and enabling one to make and use it").

reducing biotech drug prices to those typical of conventional drugs following generic entry.[62]

The unique regulatory and market barriers for FOBs set them apart from conventional drugs. The distinctive chemical properties of biotech drugs are responsible for both types of problems. This section of the Article will describe and analyze the regulatory challenges and market dynamics of biotech drugs, and then assess their implications taking into account broader scientific and market trends in the biotech industry.

A. Technical Constraints on Abbreviating FDA Review of FOBs

FDA review of FOBs will center on ascertaining whether their "safety, purity and potency" are comparable to those of the corresponding brand-name drug.[63] In the case of traditional drugs, this assessment turns on the chemical identity and purity of a generic drug (i.e., whether it is "bioequivalent" and employs the "same" active ingredient), both of which involve testing methods that are accurate and precise.[64]

A comparable set of methods does not exist for biotech drugs. In particular, while it is relatively straightforward to verify the chemical identity of most biotech drugs, no tests exist for reliably determining the higher-order three-dimensional structure of protein therapeutics (the most important class of biologics), which is critical to determining their safety and potency.[65] At the same time, it is exceedingly difficult to predict whether changes in the sequence of amino acids (the chemical building blocks) of a biotech drug will have adverse impacts on its function, as even minor structural variants may or may not pose risks.[66] Similarly, seemingly minor modifications in the production process can alter the chemical structure and conformation of a biotech drug and introduce impurities that are difficult to identify, any of which could trigger life-threatening immune responses or other serious adverse consequences.[67]

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62 Calfee, *supra* note 4, at 2 (making that case that "The biologics market will likely never resemble the simple world of traditional generics").

63 Pub. L. 111-148, § 7002.

64 21 U.S.C. § 355(j).

65 Dudzinski et al., *supra* note 29, at 847.

66 Huub Schellekens, *Biosimilar Therapeutics—What do We Need to Consider?*, 2 NDT Plus Supp. 1 i27, i28–i29 (2009), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2638545/pdf/sfn177.pdf (describing how minor process changes led to dramatic changes in the protein therapeutic EPO).

67 Kuhlmann & Covic, *supra* note 28.

Recognizing these uncertainties, the abbreviated FDA review process Congress enacted for FOBs uses "biosimilarity," a weaker standard than bioequivalence, to assess whether the safety and potency of an FOB is comparable to the name-brand drug. The weakened standard has obvious benefits for FOB manufacturers, but these benefits must be balanced against the potential risks to the public. Less obviously, the biosimilarity standard will have indirect effects on the brand-name manufacturer insofar as it permits substantial structural variation of FOBs relative to the corresponding brand-name drug.

Legal gaps have contributed to these technical barriers. Until passage of the Health Care Reform law, no abbreviated FDA approval process existed for FOBs, as FDA's abbreviated approval process for generic drugs under the Hatch-Waxman Amendments does not cover most biologics.[68] This is not simply a legislative oversight—as indicated above, an abbreviated process for FOBs will differ substantially from the process for generics. FDA will require substantially more data than it does for conventional generics,[69] including human clinical trials, which will increase the development times for and costs of commercializing FOBs.[70] Elevated FDA scrutiny could also limit production of FOBs to the larger firms, as only they will be in a position to absorb the higher upfront costs of commercializing an FOB.[71]

The heightened regulatory barriers for FOBs will be reinforced by the complexity of manufacturing them.[72] These technical challenges create two major obstacles for potential generic producers. First, the high cost of con-

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68 Calfee & DuPre, *supra* note 5, at 1303.

69 Janet Woodcock et al., *The FDA's Assessment of Follow-On Protein Products: A Historical Perspective*, 6 NATURE REV. DRUG DISCOVERY 437, 438 (2007). For some biologics (e.g., monoclonal antibodies), experts predict that "it will be many years before any sort of follow-ons for these drugs appear, regardless of patent expirations." Calfee, *supra* note 4, at 3.

70 Lanthier, *supra* note 5, at 734, 736 (concluding that "follow-on proteins are likely to be significantly more costly to develop than are small-molecule generic drugs" and estimating that development times are likely to be five to eight years versus one to two years for traditional small-molecule drugs); Grabowski, *supra* note 19, at 447 (predicting that generic biologics will require some testing in humans, which will dramatically increase fixed development costs).

71 Harbour, *supra* note 27, at 18–19.

72 Harbour, *supra* note 27, at 5 (observing that "[b]iologics are expensive, in part, because they cost so much to develop and manufacture"); John E. Calfee et al., *An Exploratory Analysis of Pharmaceutical Price Disparities and Their Implications Among Six Developed Nations* 1–2, 16 (AEI-Brookings Joint Center for Regulatory Studies, Working Paper 06-07) *available at* http://reg-markets.org/admin/authorpdfs/redirect-safely.php?fname=../pdffiles/WP06-07_FINAL.pdf (commenting that "manufacturing costs are typically much higher for biotechnology drugs"); Bruce S. Manheim et al., *'Follow-On Biologics': Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFAIRS 394, 397 (2006).

structing and operating manufacturing facilities add to the costs of market entry. Second, it is virtually impossible to replicate the processes used to make biologics, and in this sense "the process is the product." Regulatory approval will therefore be inextricably tied to the manufacturing processes because subtle, but nonetheless clinically significant, differences in a biotech drug are difficult to detect, and these obstacles will add further to the regulatory costs of FOBs.[73]

Establishing an "abbreviated" FDA approval process is therefore only a partial solution to much deeper regulatory challenges. Because of this, the BPCI subtitle is unlikely to lead either to entry of large numbers of generic producers[74] or to dramatic reductions in the pricing of biologics after patent protection and data exclusivity lapse,[75] at least in the near term. The smaller market sizes of many biologics will compound these dynamics, as smaller markets on average attract fewer competitors.[76]

Recent studies have developed models to estimate the number of FOB producers and price reductions of biologics once FOB entry occurs. Using conservative R&D costs assumptions for drugs with mid-level markets (i.e., approximately $500 million annually), one study estimated that the average number of FOB entrants would be just two, as opposed to nine for conventional drugs, and that on average FOB prices would remain at eighty-two percent of the brand price.[77] Other studies have predicted price drops for FOBs of just ten to thirty percent from the brand-name prices.[78]

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73 Harbour, *supra* note 27, at 6 (describing how even slight changes, even of equipment or facilities, can have significant impacts of safety and efficacy, and these molecular changes may not be detectable using standard analytical methods); Calfee, *supra* note 4, at 2 (arguing that while methods will likely improve in the future, "subtleties such as protein folding, which can strongly alter a biologic's effects in the body, will make that goal elusive for some time"); Manheim, *supra* note 72, at 397 (concluding that it is "virtually impossible for a follow-on company to show that its product is identical to an innovator's [biologic] product"); Woodcock, *supra* note 69, at 438.

74 Calfee, *supra* note 4, at 2 (arguing that those who assume establishing a path for FDA approval of FOBs will "dramatically reduce drug prices . . . are wrong"); *see also* Grabowski, *supra* note 19, at 448.

75 Calfee & DuPre, *supra* note 5, at 1303 (arguing that FOBs "will exert no more than a modest effect on post patent prices of targeted large-molecule drugs"); Harbour, *supra* note 27, at 18–19 (suggesting that FOBs may not meaningfully reduce prices).

76 Grabowski et al., *supra* note 19, at 440 (suggesting that large differences in levels of entry between large and small markets, with the latter much less likely to have many entrants).

77 *Id.*

78 Alexis Ahlstrom et al., *Modeling Federal Cost Savings from Follow-On Biologics*, Avalere 9 (April 2007), *available at* http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf.

These dynamics have led a number of commentators to conclude that, even once an abbreviated FDA approval process for FOBs is instituted, markets for biologics will be far less competitive than those of conventional drugs.[79] Put another way, patents and data exclusivity will be two among several barriers that limit market competition for biologics. Further, because biologics often will not be subject to brand-to-brand competition,[80] the limited competition from FOBs, will put biologics producers in a strong position to retain high prices indefinitely. For similar reasons, one would also expect, as is already evident, that brand-name biologics will command high price premiums.[81] Perhaps the only upside to this market power is that it gives producers an incentive to conduct R&D on additional uses of a drug, as there is little risk of competitors threatening their ability to recoup these added costs.[82]

B. Market Conditions and Incentives for Biotech Drugs

The predictions described above should not be read to imply that brand-name biotech drugs will be free of competitors. Where the potential markets are large—whether because the patient population is large, high price premiums can be sustained, patients must take the drug for extended periods of time, or some combination of these factors—competitors will seek out other closely related targets to develop competing brand-name drugs. This is precisely what has occurred with the specialized breast cancer drug Herceptin, which now competes with the drugs Iressa and Tarceva, both of which target different, closely related receptors.[83]

The economic significance of data exclusivity will therefore depend on the market size of a biotech drug. Drug markets can be divided roughly into three categories: (1) blockbuster drugs with sales that exceed $1 billion annually, (2) mid-range drugs with sales between $1 billion and $250 million annually, and (3) small-market drugs with sales below $250 million annually. For block-

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79 Grabowski et al., *supra* note 19, at 448–49; Calfee & DuPre, *supra* note 5, at 1303.

80 Calfee et al., *supra* note 72, at 16.

81 Calfee & DuPre, *supra* note 5, at 1307 (predicting that "we can expect rapid accretion of what might be called QALY-driven drugs: drugs that provide large benefits . . . but at high prices and, often, significant total expenditures").

82 *Id*. at 1305. For example, Avastin, which was originally approved for colorectal cancer, is being aggressively studied for its effectiveness against twenty other cancers. Calfee, *supra* note 4, at 4; Calfee & DuPre, *supra* note 5, at 1304, 1306. Similarly, Remicade is now approved for treatment of Crohn's disease, arthritis, and colitis. *Id.* at 1303.

83 *Id.* at 1306. Intense brand-to-brand competition has emergered for recombinant insulin, growth hormone drugs, Intron A® and Roferon A®, as well as Peg-Intron A® and Pegasys®.

buster drugs, brand-to-brand competition is likely to dominate—despite patents or data exclusivity—as the large market size will support multiple independently developed drugs. The blockbuster drug erythropoietin (EPO), an anti-anemia drug, illustrates this point—multiple variants of and alternatives to EPO are in various stages of development.[84] By contrast, competition in markets for drugs with annual revenues below $250 million will attract few, if any, competitors, whether from FOBs or other brands. In this context, data exclusivity will be redundant and thus have little or no effect on FOB market entry.[85]

Data exclusivity will have the greatest impact on the economics of biotech drugs with large or mid-range markets. While brand-to-brand competition in large markets is likely to dominate, data exclusivity will protect innovators from direct copy-cat competition that could occur earlier and further reduce profits. Similarly, for drugs with mid-range market sizes that are sufficient to support FOB competition, but not so large that brand-to-brand competition is likely to be significant, data exclusivity will delay the onset of this competition.

Even when FOBs are the only source of competition, however, their impact on drug prices is likely to be modest. If the available projections are correct and only 2–3 FOBs enter these markets, economic models suggest that prices will drop on average by only about twenty percent.[86] At least in the near term, this would translate into a very minor drop in prescription drug expenditures, particularly as biotech drugs generate about fourteen percent of the total revenues for pharmaceuticals, which in turn account for only about ten percent of total health care costs.[87]

Viewed from the standpoint of the innovating companies, the economic impacts of the new abbreviated FDA review process for FOBs are quite different. Drug development costs are at best diversified across a portfolio of products. But far from diluting the impact of drug revenues, the low success rate of drug development—only about one to two drug candidates out of ten that enter

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84 Iain C. MacDougall, *Novel Erythropoiesis-Stimulating Agents: A New Era in Anemia Management*, 3 CLIN. J. SOC. NEPHROLOGY 200, 200 (2008), *available at* http://cjasn.asnjournals.org/cgi/reprint/3/1/200.pdf.

85 Small-market biotech drugs are also of marginal importance economically. Sales of biologics are highly skewed. Twelve biologics with sales that exceed $1 billion account for a disproportionate share of the total revenue from all biologics; just twenty-nine biologics have sales that exceed $250 million and collectively account for ninety percent of the revenue from biologics. Lanthier, *supra* note 5, at 734.

86 Grabowski et al., *supra* note 19, at 446–47.

87 FTC, *supra* note 7, at 3; Cutler, *supra* note 25, at 1293.

clinical trials are ever commercialized[88]—leverages profits from the few drugs that are commercialized. Moreover, among the drugs that are commercialized, economic analyses estimate a mere thirty percent achieve revenue levels that exceed their costs of development.[89]

The economic viability of drug makers is dependent on, and thus highly sensitive to, the small subset of drugs that generate significant revenues, which will be negatively impacted by the lower prices and diminished market share that follow FOB entry. Because their markets are by definition relatively large, it is the subset of profitable drugs that are most likely to be impacted by FOB entry and thus most sensitive to the term of data exclusivity. Further, because the up-front costs of drug development are so great, annual sales on successful drugs must be sufficient to overcome the large capital costs. Under these circumstances, compound interest operates in reverse on capital costs of hundreds of millions of dollars—the negative equivalent, roughly speaking, of a mid-sized university endowment for each drug in development.

The economic drag associated with R&D costs is evident in the high sensitivity of drug cost recovery to the duration of the data exclusivity term. Taking into account the heightened barriers to entry of FOB manufacturers, economic models find that brand-name drug makers could not recoup their costs if the data exclusivity term were much less than ten years.[90] In other words, if revenues are not sufficient to overcome the high upfront costs, drug companies will not be able to obtain sufficient returns for investors. This would put them in a position analogous to that of a consumer who is only able to make interest payments on a large credit card debt.

Patient access to drugs, by contrast, is unlikely to be affected much by the specific duration of data exclusivity. Particularly with the expanded coverage established under the new Health Care reform law, drug purchasing will typically be mediated by insurance companies. Patients generally will not be

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88 Jeffrey Mervis, *Productivity Counts—But the Definition Is Key*, 309 SCIENCE 726, 726–27 (2005) (discussing the declining success rates of drugs entering clinical trials); F.M. Scherer, *Uncertainty and Choice: The Challenges of Pharmaceutical Efficacy, Safety, and Cost*, 28 MANAGERIAL DECISION ECON. 267, 271 (2007) (highlighting the that fact that "Seven products out of ten failed to return average R&D costs").

89 Grabowski, *supra* note 2, at 484.

90 *Id*. at 486–87; Henry Grabowski, Genia Long & Richard Mortimer, *Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques* 28–29 (Duke U. Dep't of Econ. Working Paper, No. 2008-10), *available at* http://econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf. *But cf.* Brill, *supra* note 20, at 3 (arguing that "seven years of data exclusivity would be sufficient in maintaining strong incentives to innovate while fostering a competitive marketplace").

subject to the full cost of drugs, or their capacity to afford biotech drugs will not be affected by whether or not FOBs are available—they will be priced out of the market either way. Similarly, for most insurance policies price differentials of 10–30 percent on drugs that cost tens of thousands of dollars per treatment regime are unlikely to have much effect on patient access. Either the high cost of the drug will be justified (perhaps given the costs of alternative interventions), or their costs will far exceed lower-cost options (or the limitations of an insurance plan) whether or not FOBs are available.

On its face, our conclusion that a shortened data exclusivity period is likely to reduce the profits of biologic innovators, and hence the incentive for biologic innovation, while at the same time producing minimal cost savings for consumers might seem contradictory. Above all, it turns on the sensitivity of biotech drug revenues to the duration of the data exclusivity term, which is itself driven by the biotech industry's high cost of capital and related sensitivity to near-term profit margins.[91] This contrasts the low sensitivity of the industry's profitability to market penetration levels of FOBs and, to a lesser extent, projected drops in biologics prices following twelve years of data exclusivity.[92] These results, which would benefit from further study, suggest that shortening the duration of data exclusivity, and thus lowering near-term drug costs, may heighten tensions between patient access and sustaining biotech innovation, relative to policies designed to promote rapid FOB entry and competition after data exclusivity ends.

It is also important to recognize that while market entry by a competing FOB will inevitably divert sales from the innovator, it will not benefit consumers if the price of a biologic drug does not drop significantly as a result of this competition. The innovator's lost profits could simply be diverted to the FOB manufacturer, with little or no resulting savings for consumers.

The holding in a recent federal case illustrates this point. The judge entered a preliminary injunction blocking market entry of a competing biotech drug after determining that it would reduce the innovator's profits, but was un-

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91 Grabowski, Long & Mortimer, *supra* note 90, at 16–17.

92 *Id*. at 39. For a twelve-year data exclusivity period, Table 5 reveals very little change in the estimated time for a company to breakeven (14.4 versus 14.6 years) across FOB market shares ranging from twenty-five to fifty-five percent. *Id.* Similarly, even for the highest level of FOB market share (fifty-five percent), shifting from an assumed price drop of ten percent in the first year following the end of data exclusivity and twenty-five percent in the fourth year and beyond to an assumed price drop of twenty and forty percent, respectively, merely increased the time to breakeven by about five years or thirty percent. *Id.* These differentials are dramatically different than the twenty-plus years need to breakeven projected for shorter data exclusivity periods. *Id.*

likely to cause a drop in the price Medicare pays for the drug.[93] In reaching this conclusion, the court credited the testimony of a Stanford economics professor, who explained that competition in the market for the biotech drug at issue, an anti-anemia agent, bears little resemblance to "plain vanilla" competition in an open market.[94] Like most biologic drugs, this one was dispensed by physicians and the purchaser was the physician or healthcare provider.[95] The economist testified that the incentives under the Medicare program undermine price competition, and might actually lead to higher prices following entry of a competitor.[96] Under these circumstances, sales diverted from a brand-name drug to a competing FOB serve only to reduce innovator profits, and thus the incentives for innovation, without benefiting patients.[97]

C. Promoting Competition in Markets for Biotech Drugs

The successes of biomedical innovation are paradoxically at the root of the health care crisis.[98] The better technologies become, the more people want access to them and the more total health care costs grow.[99] Yet, private investment in biomedical research and development will unavoidably be affected by government policies—smaller markets for products will reduce incentives to invest.[100] A central challenge for policymakers will be to contain costs without

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93 Amgen, Inc. v. F. Hoffman-La Roche Ltd., 581 F. Supp. 2d 160 (D. Mass. 2008), *vacated in part on other grounds*, 580 F.3d 1340 (Fed. Cir. 2009). Medicare ultimately pays for most of the drug (ESA) used in this country.

94 *Id.* at 219.

95 *Id.* at 217–18.

96 *Id.* at 221–22.

97 *Id.* at 226–27.

98 James J. Mongan et al., *Options for Slowing the Growth of Health Care Costs*, 358 N. ENG. J. MED. 1509, 1509 (2008) ("the primary driver of cost increases is technological progress," and yet "we want cost control, but we also want broad access to health care and continued innovation"); Thomas Bodenheimer, *High and Rising Health Care Costs. Part 2: Technologic Innovation*, 142 ANNALS OF INTERNAL MED. 932, 932 (2005), *available at* http://www.annals.org/content/142/11/932.full.pdf ("Most, if not all, economists and policy analysts believe that technologic advance is a key driver of health expenditure growth.").

99 Annetine C. Gelijns et al., *Evidence, Politics, and Technological Change*, 24 HEALTH AFFAIRS 29, 32 (2005), *available at* http://content.healthaffairs.org/cgi/reprint/24/1/29.pdf ("Because technological change often reduces cost per patient and improves quality, thereby expanding demand, improvements in efficiency do not necessarily yield global cost savings").

100 Henry J. Aaron, *Health Care Rationing: Inevitable but Impossible?*, 96 GEO. L.J. 539, 547 (2008) ("By curtailing the size of the market for medical innovation, rationing would alter the financial incentives that guide investments in medical R&D"); Cutler & McClellan, *supra*

unduly slowing innovation.[101] This tradeoff is particularly significant for pharmaceuticals, which are both costly to develop and have been shown to generate social returns that are often several times that of their private value.[102]

The Hatch-Waxman Amendments to the FDCA have demonstrated that enhancing competition is an effective, minimally intrusive way to reduce the costs of conventional drugs. Unfortunately, implementing Hatch-Waxman-like policies for FOBs is complicated by the barriers to entry discussed above. Moreover, simply reducing FDA regulatory costs will not be sufficient. The smaller average market sizes for biotech drugs relative to conventional pharmaceuticals complicates the economics by exacerbating tensions between sustaining profits sufficient to support innovation and ensuring patient access to new drug products.

The focus of the debate over FOB policies on the duration of data exclusivity ignores these fundamental differences. It also could be counterproductive for everyone. Owing to the large upfront costs of drug development and high costs of capital for the industry (and particularly for biotech startups),[103] the optimal temporal profile of drug prices may favor high initial prices followed by a significant drop after patent protection (or data exclusivity) ends. Economists have estimated that capital costs account for close to fifty percent of the total costs of drug development,[104] making them the single largest cost contributor. More importantly, the high costs of capital, particularly relative to the public

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note 11, at 13 (arguing that even "waste reduction must be balanced against the potential for less rapid technical innovation").

101 Carl Nathan, *Aligning Pharmaceutical Innovation with Medical Need*, 13 NATURE MED. 304, 304 (2007); Shelby D. Reed et al., *How Changes in Drug-Safety Regulations Affect the Way Drug and Biotech Companies Invest in Innovation*, 25 HEALTH AFFAIRS 1309, 1315 (2006), *available at* http://content.healthaffairs.org/cgi/reprint/25/5/1309 (arguing that "reductions in drug industry profits, achieved through price controls, could have a sizeable impact on R&D investment, leading to fewer breakthrough therapies in the future"); Frank & Newhouse, *supra* note 11, at 39 (arguing that "Any proposal to alter approaches to setting prices for prescription drugs must recognize the threat posed to research and development (R&D) incentives and the industry's ability to attract capital").

102 Frank & Newhouse, *supra* note 11, at 39 (stating that "Pharmaceutical R&D has produced enormous economic value in recent decades"); Cutler, *supra* note 25, at 1293 (describing studies finding the average cost of a quality-adjusted life year (QUALY) for drugs to be $11,000, as opposed to $140,000 per QUALY for medical procedures).

103 Grabowski et al., *supra* note 91, at 16–17; NAT'L VENTURE CAPITAL ASS'N, THE IMPORTANCE OF EVALUATING THE COST OF CAPITAL FOR EARLY-STAGE BIOTECHNOLOGY VENTURES TO PRESERVE INNOVATION (2009), http://www.nvca.org/index.php?option=com_docman&task=doc_download&gid=467&ItemId=93.

104 DiMasi & Grabowski, *Cost of Biopharmaceutical R&D*, *supra* note 12, at 475–76.

sector, favor drug pricing regimes that allow upfront investments to be recouped sooner to lower the overall costs. Contrary to convention wisdom, over time this strategy could help to mitigate the tensions between patient access and promoting biotech innovation.

The implicit tradeoff here is temporal, that is between patients subject to the high prices of drugs sold under patent or protected by data exclusivity and those patients who benefit from greater access after such protection ends. There is no simple means of resolving this tradeoff. However, our analysis shows that whether data exclusivity spans seven or twelve years would, on its own, have little effect either way. In the absence of effective policies to promote entry of FOB manufacturers after patent protection or data exclusivity terminate, the benefits of the new abbreviated FDA process for FOBs will be limited irrespective of these timing issues.

We can propose only a rough set of policies to mitigate the remaining barriers to FOB entry. Calibrating policies, insofar as it is possible, would require a much greater understanding of the economics of drug innovation and knowledge about interactions between potential policies. The Orphan Drug Act (ODA),[105] which was passed in 1984, is one of the best examples of a coordinated, multipronged approach to promoting innovation. As its title suggests, the ODA focuses on rare diseases for which patient populations are insufficient to justify the large costs of drug development. The ODA incorporates an eclectic mix of policies, including regulatory streamlining, tax incentives, technical support, and direct subsidies.[106] However, despite its broadly acknowledged success promoting development and commercialization of small-market drugs,[107] there is little evidence that Congress assessed the relative strengths and weaknesses of the policies incorporated in the ODA or their relative efficiency. In fact, surprisingly few studies—economic or otherwise—have been conducted to assess the relative virtues of different innovation policies.

Promoting entry of FOBs will also require development of several coordinated policies. The multiple market complications at issue—technology spillovers, obdurate technical uncertainties, smaller market sizes, high regulatory costs—require distinct policies to address them. Similar to the ODA, this is likely to require a mix of technical support to minimize the testing required un-

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105 Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa–ee (1998)).

106 David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses*, 31 AM. J.L. & MED. 365, 369–74 (2005).

107 Wesley Yin, *Market Incentives and Pharmaceutical Innovation*, 27 RES. POL. 1060, 1061–62 (2008).

der the abbreviated FDA approval process, tax incentives to overcome the higher costs of plant construction, and publicly funded basic research to address the scientific impediments to developing low-cost and reliable test methods for evaluating biosimilarity.

In other areas of technological development, economists are beginning to evaluate the benefits of combining complementary policies when several types of market failure are present.[108] The approach that we are advocating here—one that also combines a mix of measures ranging from patents to direct subsidies—would greatly benefit from economic analyses on the specific combinations of policies likely to be most effective given this set of market barriers. While this work may not resolve the specific magnitudes of incentives or funding for basic research needed, they could provide valuable insights on the relative efficiency of different mixes of policies.

The passage of the BPCI subtitle in the Health Care Reform law may be reflective of broader trends that are eroding the importance of patents in the biomedical sciences. Policy debates nevertheless remain fixated on patents and their regulatory analogues. This is perhaps understandable from a purely political perspective because these other policies and problems raise less tractable technical and legal challenges. Yet, the mix of market failures and barriers that exist cannot be solved by patents alone; only a multifaceted approach that combines policies will succeed. As it stands, the abbreviated FDA approval process for FOBs established in the Health Care Reform law will not come close to the success of the abbreviated process for convention drugs in the Hatch-Waxman Amendments. Congress must address the remaining barriers to market entry of FOBs in order for this earlier success to have a chance of being replicated for the new generation of biologic drugs.

IV. CONCLUSIONS

The costs of health care in the United States are approaching the outer bounds of what is sustainable. Health care spending was projected to reach $2.4 trillion in 2008, or about sixteen percent of U.S. gross domestic product.[109] The emergence and rapid growth of biotech drugs will further strain the system given their technical complexity, typically modest market sizes, and relatively high

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[108] *See, e.g.*, Carolyn Fischer & Richard G. Newell, *Environmental and Technology Policies for Climate Mitigation*, 55 J. ENVTL. ECON. MGMT. 142, 144 (2008).

[109] HENRY J. AARON & JOSEPH P. NEWHOUSE, THE BROOKINGS INST., MEETING THE DILEMMA OF HEALTH CARE ACCESS 1 (2008), *available at* http://www.brookings.edu/papers/2007/~/media/Files/Projects/Opportunity08/PB_HealthCareAccess_Aaron.pdf.

costs of production. The often stunning costs of biotech drugs have rightfully caught the attention of Congress, but the focus of the debate on data exclusivity obscured these other critical factors. On balance, we find reasonable grounds for a twelve-year term of data exclusivity for biotech drugs, but this issue is ultimately secondary. Unless the remaining barriers to entry of FOBs are addressed, the new abbreviated FDA approval process will have far less of an impact on biotech drug prices than the one for conventional drugs. Designing effective policies to overcome these barriers warrants much greater attention and careful economic analysis than it has received to date.