

MISPLACED FEARS IN THE LEGISLATIVE BATTLE OVER AFFORDABLE BIOTECH DRUGS

David E. Adelman and Christopher M. Holman

Much like tort reform, the debate over pending legislation on biotech drugs—and particularly regulatory supplements to patent protection—has taken on a significance that dwarfs its impact on overall health care expenditures. This article examines the legal, economic, and policy dimensions of this debate. We argue that the controversy over regulatory “data exclusivity” is a sideshow and that policymakers should focus on mitigating the systemic barriers to entry that pose much greater and longer-term obstacles to lower-cost 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 significant in absolute terms.⁴ Further, with the accelerating 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 are fueling congressional interest in legislation that would create an abbreviated FDA approval process for so called “follow-on biologics” (FOBs), which are the analog of generics for biotech drugs.⁶ Legal gaps and technical differences necessitate 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 to the Food Drug & Cosmetic Act (FDCA).⁷

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, *Pharmacogenomics: A Primer for Policymakers*, National Health Policy Forum 11 (Jan. 2008) available at <http://www.nhpf.org/pdfs_bp/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 (Feb. 2009).

⁴ John E. Calfee, *Facing Reality on Follow-On Biologics*, *Health Policy Outlook* 1 (April 2007) available at <http://www.aei.org/publications/pubID.26010/pub_detail.asp>.

⁵ Michael Lanthier, et al., *Economic Issues with Follow-On Protein Products*, 7 *NATURE REV DRUG DISCOVERY* 733, 733 (2008); see also John E. Calfee & Elizabeth DuPre, *The Emerging Market Dynamics of Targeted Therapeutics*, 25 *HEALTH AFFAIRS* 1302, 1304 (2006) (noting biologics resistance to pricing pressures).

⁶ Note that an FOB would not be a true generic drug. Due to the complexity of biologics, an FOB would generally not be chemically identical to the original product and therefore would not be interchangeable.

⁷ Federal Trade Commission, *Emerging Health Care Issues: Follow-On Biologic Drug Competition* 3 (June 2009); Pub. L. No. 57-244, 32 Stat. 728 (1902). 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

Technically, the chemical structures of biotech drugs are much more complex than conventional drugs, which raises distinct challenges for assessing the safety and efficacy of an FOB relative to the name-brand drug on which it is based. Pending bills reflect these differences insofar as they provide 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.⁸

Proponents of new legislation claim that it will 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 pending legislation is a provision that would allow an FOB applicant to rely on data generated by the original drug maker to secure FDA marketing approval. By reducing the time for and costs of obtaining FDA approval, this provision would facilitate market entry of FOBS. Yet insofar as the policy succeeds, it would also erode the profits of the original drug producer and the market incentives for developing new drug products.¹⁰

Broad support exists for the creation of some form of abbreviated pathway for FOBs. The biotech industry's support, however, is contingent on the availability of patent protection, or a regulatory variant of it, that ensures 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—well-accepted estimates suggest that average costs of commercializing a biotech drug exceed \$1 billion, with a large fraction of it attributable to capital costs that must be borne for development periods that average twelve years.¹¹ As these qualifications suggest, the controversy over the proposed legislation centers on differing views about the appropriate balance between assuring adequate market returns to sustain innovation and minimizing the costs of biotech drugs.

One of the most contentious provisions in the pending legislation would grant an innovating company a twelve-year period of “data exclusivity” to supplement traditional patent

under the FDCA, including most notably Omnitrope, a follow-on version of recombinant human growth hormone. <http://www.lek.si/eng/media-room/press-releases/3948/>.

⁸ Christopher M. Holman, *A Response to the FTC's Report on Follow-On Biologics* at 2. (October 1, 2009) (summarizing various congressional bills and amendments that would create statutory basis for approval of follow-on biologics - some of these provisions are included in the omnibus health care reform bills recently passed in the House and Senate). Available at SSRN: <http://ssrn.com/abstract=1481350>. FOB provisions are included in Healthcare bills passed by the House of Representatives (H.R. 3962) and Senate (H.R. 3590) on November 7, 2009 and December 24, 2009, respectively.

⁹ Pedro Cuatrecasas, *Drug Discovery in Jeopardy*, 116 J. CLINICAL INVESTIGATION 2837, 2840 (2006) (describing biotech drugs with costs from about \$110,000 per year to more than \$200,000 per year).

¹⁰ David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20 HEALTH AFFAIRS 11, 13 (2001); 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).

¹¹ Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 475-76 (2007). 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); Christopher P. Adams & Van V. Brantner, *Estimating The Cost of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFFAIRS 420, 422-23 (2006).

protection, with the terms running concurrently.¹² This measure works in conjunction with the proposed abbreviated process for FOBs, which as outlined above would allow 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 would preclude 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.¹³

Importantly, data exclusivity would neither create restrictions on the use of the drug itself, nor would 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, 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, the pending Health Care Reform legislation affords FOB producers substantial leeway to modify production processes and the chemical structure of biologics themselves.¹⁴ The FOB provisions in the pending legislation create an abbreviated pathway for "biosimilar" variants of a brand-name drug—chemical identity is not required. This added flexibility would enhance 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.

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 would mitigate such deficiencies.¹⁵ 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.¹⁶

The biotech industry has countered 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

¹² The FOB provisions included in the Healthcare bills recently passed by the House of Representatives (H.R. 3962) and Senate (H.R. 3590) both provide twelve years of data exclusivity for innovators. Some earlier proposed FOB bills would provide a substantially shorter data exclusivity period. Holman, *supra* note 8, at 3 (H.R. 1427 would provide only five years).

¹³ *Id.*

¹⁴ Holman, *supra* note 8, at 9.

¹⁵ FTC, *supra* note 7, at iii-viii.

¹⁶ Henry G. Grabowski, et al., *Entry and Competition in Generic Biologics*, 28 *MANAGERIAL DEC. ECON.* 439, 440 (2007).

data exclusivity is essential to the profitability of biotech drugs.¹⁷ They argue that, contrary to critics' claims, economic projections find that FOB market barriers alone would 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 would run out at roughly the same time,¹⁸ implying that data exclusivity would rarely extend the market exclusivity of a drug maker.¹⁹ In addition, data exclusivity could encourage development of clinically important biologics that would otherwise be abandoned because robust patents on the active ingredient are unavailable.²⁰

Prevailing uncertainties provide grounds for and against Congress legislating a twelve-year term of data exclusivity for biotech drugs. What is unequivocal, though, is that the effects either way on health care expenditures would be modest. According to a 2007 estimate by the Congressional Budget Office, establishing an abbreviated FDA approval process for FOBs would reduce national spending on prescription drugs by just 0.5 percent over the first ten years of the program.²¹ The impact of a shortened data exclusivity period would be a fraction of this estimate, since competitive market entry by FOBs would still face the barriers to market entry described above. Overall the health care savings would be nominal, as drugs account for only about ten percent of total health care expenditures in the United States.²²

We will argue that, on balance, the potential benefit to patients that might result from a shortened 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.²³ More importantly, we believe that the current focus on data exclusivity is misplaced. Weak competition in markets for biotech drugs poses a much greater and longer-term problem for patient access—without robust competition, pricing of many biotech drugs will remain high indefinitely. The most important issue for Congress to address ought to be reducing the barriers to market entry for FOB manufacturers after the relevant patent terms and data exclusivity end. We close by suggesting a variety of ways in which this objective could be met.

I. 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

¹⁷ *Id.*; Grabowski, *supra* note 2, at 479; *cf.* Alex M. Brill, *Proper Duration of Data Exclusivity for Generic Biologics: A Critique* (November 2008) (arguing that seven years of data exclusivity would provide sufficient incentives) available at <http://www.tevadc.com/Brill_Exclusivity_in_Biogenics.pdf>.

¹⁸ 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. Grabowski, *supra* note 2, at 493.

¹⁹ Holman, *supra* note 8, at 6.

²⁰ *Id.* at 7.

²¹ Congressional Budget Office, Cost Estimate for S. 1695: Biologics Price Competition and Innovation Act of 2007 1 (June 27, 2007); *see also* Lanthier, *supra* note 5, at 736.

²² David M. Cutler, *The Demise of the Blockbuster?*, 356 *New Eng. J. Med.* 1292, 1293 (2007).

²³ Data exclusivity also ensures parity with traditional drugs, which benefit from patent terms that are comparable to the twelve-year term being proposed. Henry G. Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 28 *Managerial & Decision Econ.* 491, 4493 (2007).

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 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.²⁴ 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.²⁵ At the same time, scientific understanding of the relationship between structure and function in a biotech drug is still only partially understood.²⁶ 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.²⁷

The complexity of biotech drugs creates two mutually reinforcing problems for innovators. The size and complexity of biotech drugs affords competitors many molecular degrees of freedom, which opens up many 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.

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.

²⁴ Pamela Jones Harbour, FTC Commissioner, *The Competitive Implications of Generic Biologics* 14 (Jun. 2007) 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).

²⁵ Congressional Research Service, *Follow-on Biologics: Intellectual Property and Innovation Issues*, RL33901 2 (Jan. 2008). 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; Martin Kuhlmann & Adrian Covic, *The Protein Science of Biosimilars*, 21 [Supp. 5] Nephrol. Dial. Transplant. v4 (2006).

²⁶ David M. Dudzinski, et al., *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 New Eng. J. Med. 843, 847 (2008).

²⁷ Kuhlmann & Covic, *supra* note 24.

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 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.²⁸ The results invert for the 23 patent litigation cases involving other types of patents (e.g., specific formulations, uses, or processes of manufacture), the brand-name company never prevailed in court, while the generic challenger won 13 of the cases, and 10 cases settled out of court.²⁹

The limitations of patents on biotech drugs became evident with the first generation of compounds discovered (e.g., insulin).³⁰ 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.³¹

This basic scenario continues to stoke fears about the legislation pending in Congress. Industry concern is heightened by provisions in the legislation that would 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.

²⁸ Bernstein Global Wealth Management, Paragraph IV Litigation: A Guide for the Perplexed 6 (October 2007) (hereinafter “Bernstein Report”).

²⁹ *Id.* at 6.

³⁰ *Genentech v. Wellcome*, 29 F.3d 1555 (Fed. Cir. 1997); *Hormone Research Center v. Genentech*, 904 F.2d 1558 (Fed. Cir. 1990).

³¹ Christopher M. Holman, “Learning from Litigation: What Can Lawsuits Teach Us About the Role of Human Gene Patents in Research and Innovation?” 18 KANSAS J.L. PUB. POLICY 215, 223-29 (2009).

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 might 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.³²

The history of cases involving enforcement of composition-of-matter patents on biotech drugs paints a decidedly negative picture. There does not appear to be a single appellate-level decision in which a patent on the active ingredient of a biotech drug has been found valid and infringed.³³ At the district court level, infringement of a valid composition-of-matter patent has been found twice,³⁴ but both are recent decisions involving a family of related patents claiming variations of Amgen’s blockbuster drug erythropoietin.³⁵ 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 at the time this article is being written the decision has yet to be affirmed on appeal.³⁶ Similarly, the district court’s decision on patent validity in *Amgen v. Hoffman-La Roche* was recently vacated and remanded for reconsideration.³⁷ In response, Amgen and Hoffman-La Roche settled their dispute, so no appellate decision will be forthcoming in this case either.³⁸

While composition-of-matter patents have often proven ineffective in protecting biotech drugs, patentees have had 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.³⁹ Amgen’s successful enforcement of patents covering genes and production methods used to produce erythropoietin has been notable in this respect,⁴⁰ but numerous examples exist in which competitors have successfully designed around such patents

³² 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 28.

³³ The Court of Appeals of the Federal Circuit has found composition of matter patents claiming a biologic active ingredient not infringed by a competing product. See, e.g., *Amgen v. Hoechst Marion Roussel*, 457 F.3d 1293 (Fed. Cir. 2006) (U.S. Patent No. 5,621,080, claiming recombinant erythropoietin, not infringed by competing recombinant erythropoietin product) and *Genentech v. Wellcome Foundation*, 29 F.3d 1555 (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).

³⁴ *Amgen v. Hoffman-La Roche*, 581 F.Supp.2d 160 (D.Mass. 2008); *Amgen v. Hoechst Marion Roussel*, 579 F.Supp.2d 199 (D.Mass. 2008).

³⁵ FTC article at 10.

³⁶ 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).

³⁷ *Amgen v. Hoffman-La Roche*, Doc. No. 2009-1020, -1096 (Fed. Cir. Sept. 15, 2009) (the district court’s judgment that the COM claims were infringed was affirmed).

³⁸ *Amgen v. Hoffman-La Roche*, Doc. No. 05-12237, Document 1775, Stipulation and Order (Dec. 22, 2009).

³⁹ Holman, *supra* note 36, at 295.

⁴⁰ *Id.* at 295, 329-30.

and avoided infringement liability.⁴¹ Even critics of using data exclusivity to augment patent protection acknowledge this vulnerability to simple design-around strategies.⁴²

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.⁴³ 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.⁴⁴ 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”). 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 successfully enforced broad patent claims encompassing numerous variants of basic gene or protein structures.⁴⁵

Unfortunately, these findings have been misinterpreted by critics of data exclusivity. They 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 that accepted claiming strategies exist that can ensure adequate patent coverage.⁴⁶

Although 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, only one, *Regents of the University of California v. Eli Lilly*,⁴⁷ 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

⁴¹ Holman, *supra* note 31, at 215, 223-29.

⁴² FTC, *supra* note 7, at 45

⁴³ Holman, *Learning from Litigation*, *supra* note 41, at 229-31.

⁴⁴ 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 (collecting law review articles and judicial decisions expressing view that written description requirement substantially limits effective scope of patent protection available for biotechnology inventions).

⁴⁵ *Id.* (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.

⁴⁶ FTC, *supra* note 7, at iii-viii, 36-37.

⁴⁷ 119 F.3d 1559 (Fed. Cir. 1997).

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).⁴⁸

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.⁴⁹ 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 1999.⁵⁰ The revised guidelines raise the written description requirement for biotechnology inventions, making it distinct from and more restrictive than the enablement requirement for patentability.⁵¹ Moreover, because of the underlying unpredictability of structure-function relationships for biotech drugs, the revised guidelines will 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.⁵²

The recent BPAI decision in *Ex parte Kubin* is representative of the shifting doctrines relevant to the scope of patent claims on biotech patents.⁵³ 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

⁴⁸ 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.

⁴⁹ FTC, *supra* note 7, at 36-37.

⁵⁰ PTO, Written Description Training Materials (March 2008) *available at* <http://www.uspto.gov/web/menu/written.pdf>.

⁵¹ PTO Issues Revised Written Description Guidelines, Further Muddying the Waters, *available at* <http://holmansbiotechblog.blogspot.com/2008/04/pto-issues-revised-written-description.html>.

⁵² Based on conversations with patent attorneys working in this area.

⁵³ 83 U.S.P.Q.2d 1410, 2007 WL 2070495 (BPAI 2007).

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 may soon be reinforced by the Federal Circuit, which recently agreed to reconsider the written description doctrine en banc.⁵⁴ It remains unclear what direction the Court will take, as there are signs that it could move to substantially curtail, or perhaps even jettison, the heightened written description requirement, and others that it will merely clarify how it is to be applied. Irrespective of the direction the Federal Circuit takes, the enablement requirement for patentability would serve as a powerful limit on the scope of patent protection available for biotech drugs. Further, the Federal Circuit has placed a renewed emphasis on the enablement requirement that has reinvented it as a primary doctrinal limit on claim scope.⁵⁵

The uncertain 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 systemic limitations of composition-of-matter patents on biotech drugs, even patents with broad claims will be relatively easy to circumvent because of the huge number of structural variants that exist for biotech drugs given the large size of their active compounds. This point is of particular importance for the proposed legislation in Congress, 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 covered by the weaker “biosimilarity” standard that has been proposed for the abbreviated FDA approval process for FOBs.

II. 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 the technical challenges of manufacturing them. The resulting added costs increase barriers to market entry for FOB manufacturers. By contrast, FDA review of generic versions of traditional 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 proposed abbreviated FDA approval process for biotech drugs will not lead to FOB prices that come close to those typical for generic versions of conventional drugs.⁵⁶

⁵⁴ *Araid Pharmaceuticals v. Eli Lilly*, 2009 WL 2573004 (Fed. Cir. 2009).

⁵⁵ See, e.g., *Automotive Technologies v. BMW*, 501 F.3d 1274 (Fed. Cir. 2007); *Liebel-Flarsheim v. Medrad*, 481 F.3d 1371 (Fed. Cir. 2007); *Halliburton Energy Services, Inc. v. M-I LLC*, 514 F.3d (Fed. Cir. 2008); *Sitrick v. Dreamworks, LLC*, 516 F.3d 993 (Fed. Cir. 2008).

⁵⁶ Calfee, *supra* note 4, at 2 (making that case that “The biologics market will likely never resemble the simple world of traditional generics”).

The unique regulatory and market barriers for FOBs set them apart from conventional drugs. The distinctive chemical properties of biotech drugs create 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 an FOB will center on ascertaining whether its “safety, purity and potency” are comparable to those of the brand-name drug. 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.

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.⁵⁷ 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.⁵⁸ 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.⁵⁹

Recognizing these uncertainties, the abbreviated FDA review process Congress has proposed 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 insofar as it reduces regulatory constraints, 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 a brand-name drug.

Legal gaps have contributed to these technical barriers. No abbreviated FDA approval process exists for FOBs, as FDA’s abbreviated approval process for generic drugs under the Hatch-Waxman Amendments does not cover most biologics.⁶⁰ This is not simply a legislative oversight—an abbreviated process for FOBs will differ substantially from the process for generics. FDA will require substantially more data than it does for traditional generics,⁶¹ including human clinical trials, which will increase the development times for and costs of

⁵⁷ Dudzinski, et al., *supra* note 26, at 847.

⁵⁸ Huub Schellekens, *Biosimilar Therapeutics—What do We Need to Consider?*, 2 NDT Plus Supp. 1 i27, i28-i29 (2009) (describing how minor process changes led to dramatic changes in the protein therapeutic EPO).

⁵⁹ Kuhlmann & Covic, *supra* note 24.

⁶⁰ Calfee & DuPre, *supra* note 5, at 1303.

⁶¹ Calfee, *supra* note 4, at 3; 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.” Woodcock-07, 438.

commercializing FOBs.⁶² 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.⁶³

The heightened regulatory barriers for FOBS will be reinforced by the complexity of manufacturing them.⁶⁴ These technical challenges create two major obstacles to potential generic producers. First, the high cost of constructing 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 are difficult to detect, and these obstacles will add further to the regulatory costs of FOBs.⁶⁵

Establishing an “abbreviated” FDA approval process is therefore at best a partial solution to much deeper regulatory challenges. Because of this, it is unlikely to lead either to entry of large numbers of generic producers⁶⁶ or to dramatic reductions in the pricing of biologics after patent protection lapses,⁶⁷ 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.⁶⁸ 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., ~\$500 million annually), one study estimated that the average number of FOB entrants would be just two, as opposed to nine for traditional drugs, and that on

⁶² 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-Biologics, 447 (predicting that generic biologics will require some testing in humans, which will dramatically increase fixed development costs).

⁶³ Harbour, *supra* note 24, 19.

⁶⁴ Harbour, *supra* note 24, at 11 (observing that biologics are expensive, in part, because they cost so much to develop and manufacture”); Calfee-Villarreal, 16 (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).

⁶⁵ Harbour, *supra* note 24, 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 64, 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”); Janet Woodcock, et al., *The FDA’s Assessment of Follow-On Protein Products: A Historical Perspective*, 6 NATURE REV DRUG DISCOVERY 437, 438 (2007).

⁶⁶ 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-Biologics, 448.

⁶⁷ 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 24, at 19 (suggesting that FOBs may not meaningfully reduce prices).

⁶⁸ Grabowski, et al., *supra* note 16, 440 (suggesting that large differences in levels of entry between large and small markets, with the latter much less likely to have many entrants).

average FOB prices would remain at eighty-two percent of the brand price.⁶⁹ Other studies have predicted price drops for FOBs of just ten to thirty percent from the brand-name prices.⁷⁰

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.⁷¹ Put another way, patents will be one among several barriers that maintain the effective duration of market exclusivity for biologics. Further, because biologics often will not have competitive substitutes,⁷² limited competition from FOBs, which even when they exist often will not be perfectly interchangeable with their brand-name counterparts, will put biologics producers in a much stronger position to retain high prices indefinitely. One would also expect, as is already evident, that brand-name biologics will command high price premiums.⁷³ One 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 their costs.⁷⁴ Recent work suggests that enhanced follow-on investment is already being conducted for a number of biotech drugs.⁷⁵

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, large price premiums can be sustained, patients must take the drug for extended periods of time, or some combinations 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.⁷⁶

The impact of data exclusivity will also 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 blockbuster drugs, brand-to-brand competition is likely to dominate—despite of 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

⁶⁹ Grabowski, et al., *supra* note 16, at 440.

⁷⁰ 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>.

⁷¹ Grabowski, et al., *supra* note 16, at 448-49; Calfee & DuPre, *supra* note 5, at 1303.

⁷² Calfee-Villarreal, 16.

⁷³ 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”).

⁷⁴ *Id.* at 1305.

⁷⁵ 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 1303, 1306. Similarly, Remicade is now approved for treatment of Crohn’s disease, arthritis, and colitis. Calfee & DuPre, *supra* note 5, at 1303.

⁷⁶ Calfee & DuPre, *supra* note 5, at 1306. Intense brand-to-brand competition has emerged for recombinant insulin, growth hormone drugs, Intron A[®] and Roferon A[®], as well as Peg-Intron A[®] and Pegasys[®].

alternatives to EPO are in various stages of development.⁷⁷ 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 no effect on FOB market entry.⁷⁸

Biotech drugs with large or mid-range markets will benefit from data exclusivity. While brand-to-brand competition in large markets will still occur, data exclusivity would protect innovators from direct copy-cat competition that could dramatically reduce profits, and as a consequence incentives for innovation. 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 dominate, data exclusivity will be critically important. However even here, where FOBs are the only source of competition, the impact on drug prices would be modest. If we assume that the available projections are correct and only about 2-3 FOBs are likely to enter these markets, economic models suggest that prices will drop on average by only about twenty percent.⁷⁹ At least in the near term, this translates into a negligible impact on total health care costs, 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.⁸⁰

Viewed from the standpoint of the innovating companies, the economic implications of an abbreviated FDA review process are quite different. Drug development costs are at best diversified across a portfolio of products. However, 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 clinical trials are ever commercialized⁸¹—leverages profits on successful drugs. 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 both lower prices and diminished market share. Further, because the up-front costs of drug development are so great, annual profits on successful drugs must be sufficient to overcome the large capital costs. Under these circumstances, compound interest operates in reverse on debts 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 sensitivity of drug cost recovery to the duration of proposed data exclusivity terms. Taking into account the heightened barriers to entry of FOB manufacturers, economic models find that brand-name drug makers could not recoup their costs (including the cost of capital) if data exclusivity terms were much

⁷⁷ Iain C. MacDougall, *Novel Erythropoiesis-Stimulating Agents: A New Era in Anemia Management*, 3 Clin. J. Soc. Nephrology 200, 200 (2008).

⁷⁸ 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.

⁷⁹ Henry Grabowski, et al., *supra* note 16, at 446-47.

⁸⁰ FTC, *supra* note 7, at 3; Cutler, *supra* note 22, at 1293.

⁸¹ Jeffrey Mervis, *Productivity Counts—But the Definition Is Key*, 309 SCIENCE 726, 726 (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 fact that “Seven products out of ten failed to return average R&D costs”).

less than ten years.⁸² The reason for this is simple: if aggregate profits on a drug are not sufficient to overcome capital costs, drug companies will not be able to obtain sufficient returns to investors. In essence, drug companies would be in a position analogous to that of a consumer who is unable to do more than make interest payments and modest contributions on a large credit card debt.

The low sensitivity of aggregate health care expenditures to the presence or absence of a data exclusivity term contrasts the heavy reliance of biotech drug makers on profits from successful drugs. This disparity applies to individuals as well. Either patients will have insurance or access to government programs, and thus not be subject to the full drug price, 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 in either case. Similarly, for insurance programs with tiered prescription drug programs, 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 offset by the high costs of alternative interventions, or their costs will far exceed lower-cost options whether or not FOBs are available.

C. Promoting Competition in Markets for Biotech Drugs

The successes of biomedical innovation are paradoxically at the root of the health care crisis.⁸³ The better technologies become, the more people want access to them and the more total health care costs grow.⁸⁴ Yet, private investment in biomedical research and development will unavoidably be affected by government policies—smaller markets for products will reduce incentives to invest.⁸⁵ A central challenge will be to contain costs without unduly slowing innovation.⁸⁶ This tradeoff is particularly significant for pharmaceuticals, which are both costly

⁸² Grabowski, *supra* note 2, at 486-87; Henry Grabowski & Genia Long, *Data Exclusivity Periods for Biologics*, Duke University Department of Economics Working Paper, No. 2008-10, 28-29 (Dec. 2008); *but cf.* Brill, *supra* note 17, at 3 (arguing that “seven years of data exclusivity would be sufficient in maintaining strong incentives to innovate while fostering a competitive marketplace”).

⁸³ James J. Mongan, et al., *Options for Slowing the Growth of Health Care Costs*, 358 N. ENGL. 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 ANN. INTERN. MED. 932, 932 (2005) (“Most, if not all, economists and policy analysts believe that technologic advance is a key driver of health expenditure growth.”).

⁸⁴ Annetine C. Gelijns, et al., *Evidence, Politics, and Technological Change*, 24 HEALTH AFFAIRS 29, 32 (2005) (“Because technological change often reduces cost per patient and improves quality, thereby expanding demand, improvements in efficiency do not necessarily yield global cost savings”).

⁸⁵ Henry J. Aaron, *Health Care Rationing: Inevitable but Impossible?*, 96 GEO. L. REV. 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* note 10, at 13 (arguing that even “waste reduction must be balanced against the potential for less rapid technical innovation”).

⁸⁶ Carl Nathan, *Aligning Pharmaceutical Innovation with Medical Need*, 13 NATURE MED. 304, 304 (2007); Reed-06, 1315 (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”); 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) (arguing that “Any proposal to alter approaches to setting prices for prescription drugs must recognize the threat posed to research and development incentives and the industry’s ability to attract capital”).

to develop and have been shown to be cost effective and to generate social returns that are often several times that of the private value.⁸⁷

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. Conversely, the price benefits that could be achieved through limiting data exclusivity for biologics are nominal. Unfortunately, implementing Hatch-Waxman-like policies for FOBs is complicated by the barriers to entry for FOBs and the technical challenges of an abbreviated FDA review process. 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.

Limiting the term of data exclusivity could also be counterproductive for everyone. Although counterintuitive, safeguarding high short-term profits through a twelve-year data exclusivity term stands to mitigate the difficulties of balancing innovation and patient access. Owing to the huge upfront costs of drug development, the optimal temporal profile of drug prices arguably favors high initial prices followed by a dramatic drop after patent protection (or data exclusivity) ends. Economists have shown that capital costs account for close to fifty percent of the total costs of drug development.⁸⁸ Accordingly, drug pricing regimes that allow large upfront investments to be recouped sooner will lower the overall costs associated with drug development and thus, on balance, mitigate the need for higher drug prices.

The benefits of this strategy will vary across the biotech industry. In particular, because large drug companies spread costs and revenue across a portfolio of drug products, the benefits will be dampened by this approach to risk diversification. However, for startup companies, of which there are many in the biotech sector, earlier payback will be extremely important given their high costs of capital and the relatively quick returns that venture capitalists and other investors often demand of them.⁸⁹ 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, but it is nevertheless clear that data exclusivity, on its own, would have little effect either way.

Our analysis shows that the most important questions concern the design of effective policies to promote entry of FOB manufacturers after innovators have enjoyed a sufficient period of patent protection or data exclusivity to support robust innovation. We can only hint at potential options here, though, because structuring effective policies will require greater

⁸⁷ Frank & Newhouse, *supra* note 86, at 39 (stating that “Pharmaceutical R&D has produced enormous value in recent decades”); Cutler, *supra* note 22, 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).

⁸⁸ DiMasi & Grabowski, *Cost of Biopharmaceutical R&D*, *supra* note 11, at 475-76.

⁸⁹ See National Venture Capital Association, *The Importance of Evaluating the Cost of Capital for Early-Stage Biotechnology Ventures to Preserve Innovation* (July 2009) *available at* <http://www.nvca.org/index.php?option=com_docman&task=doc_download&gid=467&ItemId=93> .

understanding of the specific barriers to entry and consideration of how potential policies might interact and reinforce each other.

The Orphan Drug Act (ODA), which was passed in 1984, is arguably the best example that exists 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.⁹⁰ Yet, despite its broadly acknowledged success,⁹¹ there is little evidence that Congress assessed the relatively strengths and weaknesses of the policies incorporated in the ODA.

Promoting entry of FOBs will also require development of several coordinated policies. The multiple market complications at issue—technology spillovers, deep technical uncertainties, smaller market sizes, heightened regulatory costs—will often demand distinct policies to address them. Similar to the ODA, this is likely to require a mix of technical support, tax incentives, and possibly direct subsidies, as well as basic research designed to address systemic regulatory impediments, such as the absence of 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.⁹² 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 optimal mix of policies given a set of market barriers.

III. 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.⁹³ The emergence and rapid growth of biotech drugs will further strain the system given their technical complexity, typically modest market sizes, and relatively high costs of production. The often stunning costs of biotech drugs have rightfully caught the attention of Congress, but the current focus of the debate on data exclusivity misapprehends both the primary problems and the potential solutions. On balance, we find reasonable grounds for a twelve-year term of data exclusivity for biotech drugs, but this issue is ultimately secondary. The most important problem to address is the multiple barriers to entry of FOB manufacturers. Designing effective policies to overcome them warrants much greater attention and careful economic analysis, as reducing barriers to entry holds out the promise of dramatically lowering prices of biotech drugs over the long run.

⁹⁰ 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).

⁹¹ Wesley Yin, *Market Incentives and Pharmaceutical Innovation*, 27 RES. POL. 1060, 1061-62 (2008)

⁹² See, e.g., Carolyn Fischer & Richard G. Newell, *Environmental and Technology Policies for Climate Mitigation*, 55 J. ENVTL. ECON. MGMT. 142, 144 (2008).

⁹³ Henry J. Aaron and Joseph P. Newhouse, *Meeting the Dilemma of Health Care Access*, Brookings Opportunity 08 1 (2008) available at <http://www.brookings.edu/papers/2007/0228useconomics_aaron02_Opp08.aspx>.