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EXPLORATION OF POTENTIAL ECONOMICS OF FOLLOW-ON BIOLOGICS AND IMPLICATIONS FOR DATA EXCLUSIVITY PERIODS FOR BIOLOGICS

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ABSTRACT

Legislative efforts to establish an abbreviated regulatory approval pathway for follow-on biologics ("FOBs"), also referred to as biosimilars, have generated considerable attention and debate. Legislators expect FOBs to produce cost savings through competition, much like that seen in the United

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States generic pharmaceutical market. However, biologic products, which are large complex molecules, differ from pharmaceuticals in many ways, including their basic structure, composition, and their manufacturing processes. The economics behind the establishment of an FOB market involves a plethora of issues not encountered in the generic pharmaceutical marketplace. One of the most critical and controversial issues is the determination of an appropriate period of data exclusivity or data protection for a new biologic. Building on recent research by Grabowski and using contemporary models of risk and return from the finance literature, we determine that there should be 17 years of data exclusivity for new biologics.[1] In this paper, we review some of the basic economic differences between pharmaceuticals and biologics; the potential for short run cost savings from a FOB market; and the challenging patent issues biologic products encounter that make data exclusivity periods so critical. However, the main thrust of our paper is that the considerable financial risk of biotechnology Research and Development ("R&D"), and the sensitivity of R&D to expected returns, make it critical that Congress provide adequate incentives for biotech R&D through appropriate periods of data exclusivity or data protection for biologics.

I. INTRODUCTION

As Congress considers legislation to establish an abbreviated regulatory approval pathway for FOBs, a key consideration is the length of data exclusivity or data protection needed to encourage innovation. In 2008 and 2009, a number of legislative proposals sought to establish a pathway for FOBs. The bills vary in terms of their provisions for investment incentives, with the two bills introduced in 2009 varying considerably in terms of incentives for continued R&D investment.[2] Inadequate incentives would likely diminish the economic attractiveness of undertaking new biotech R&D and investment in this sector. This is the case, as we will show, because of the financial risk associated with biotech R&D[3] and the sensitivity of R&D investment to data exclusivity or data protection periods.[4] This is particularly disconcerting in light of the social benefits attributable to innovations from this

[1] Joseph Golec & John Vernon, *Financial Risk in the Biotechnology Industry: How is it Different?* 19-23 (U. Conn. Dep't of Fin. Working Paper No. 13,604, 2008) [hereinafter Golec & Vernon, *Financial Risk*].

[2] *See* Promoting Innovation & Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. (2009); Pathway for Biosimilars Act, H.R. 1548, 111th Cong. (2009).

[3] Golec & Vernon, *Financial Risk*, *supra* note 1, at 22-23.

[4] Joseph Golec, Shantaram Hegde & John Vernon, *Pharmaceutical R&D Spending & Threats of Price Regulation*, 45 J. QUANTITATIVE & FIN. ANALYSIS (forthcoming 2010).

industry.[5] It is critical that the data exclusivity periods provide adequate financial incentives to reach the socially optimal (economically efficient) balance between short and long run interests (i.e., access to existing medicines at lower prices and access to future innovations through R&D investment).

Our paper proceeds as follows: Section II provides a comprehensive overview of the major issues and challenges associated with existing bills for FOBs. It also places the regulation of biologics and pharmaceuticals into a historical context and discusses an array of background, institutional and patent provision issues. This section sets the backdrop for the rest of our paper. Section III identifies the important clinical and economic aspects of biologics. The economic dynamics of generic entry and generic price competition are discussed and we explain why experiences in the generic pharmaceutical market, particularly after Hatch-Waxman, cannot be used to project market outcomes for follow-on biologics. We discuss key structural aspects of the potential market for follow-on biologics. Section IV will then discuss investment risk profiles for biologics, including industry structure and firm size, and the capital markets for R&D finance will be considered. Based on the model developed by Grabowski, we will argue that data exclusivity periods should be approximately 17 years.[6] Section V will conclude and place our analyses more broadly within the context of national healthcare policy (both explicit and implicit) for medical, pharmaceutical, and biological research. Cost-benefit research suggests that the U.S. is investing too little in these types of health-related research activities.[7] Thus, existing proposed periods of data exclusivity, which are all less than 17 years, are inadequate from a social welfare perspective.

II. THE REGULATORY FRAMEWORK FOR BIOLOGICS, HATCH-WAXMAN AMENDMENTS, AND CURRENT BILLS FOR FOLLOW-ON BIOLOGICS

A. The History of Biologics Regulation

The history of biologics regulation is substantially different from that of drug products. Not only are most biologics approved under a different law than pharmaceuticals, but that law was not administered by the FDA until 1972.[8] The implementation of new laws since then, as well as the nature of the

[5] Frank Lichtenberg, *Sources of U.S. Longevity Increase, 1960-1997* at 16-17, (Nat'l Bureau of Econ. Research, Working Paper No. 8755, 2002).

[6] Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition*, 7 NATURE REVS. DRUG DISCOVERY 479, 485-487 (2008).

[7] *See generally* MEASURING THE GAINS FROM MEDICAL RESEARCH, 41-73 (Kevin Murphy & Robert Topel, eds., U. Chi. Press 2003).

[8] *E.g.*, U.S. Food & Drug Administration, Biologics Centennial: 100 Years of Biologics

products themselves, has led to significant differences in the regulatory approaches to drugs and biologics.

Congress first authorized the regulation of biologics in the Biologics Control Act of 1902 ("1902 Act"), in response to the deaths of several children from a contaminated diphtheria antitoxin, and required the pre-market approval of blood products and preventative treatments such as vaccines.[9] The 1902 Act gave the Treasury Department sweeping powers over pre-market facility inspections and licensing without clearly defining approval criteria. Over the years, however, the Treasury Department adopted safety and efficacy as prerequisites for product licensure.[10] Interestingly, while the definition of biologics has changed little over time, despite successive legislative amendments and reenactments, the biologics field now encompasses products that the original drafters could have never contemplated.

Congress did not authorize pre-market approval for drugs until the passage of the Food, Drug, and Cosmetic Act ("FDCA") in 1938.[11] The FDCA initially defined "drug" as any product in interstate commerce "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals or . . . intended to affect the structure or any function of the body of man or other animals"[12] – a definition that focuses on a product's intended use rather than its composition.[13] The FDCA, in contrast to the 1902 Act, was specifically intended to cover therapies for consumers who were already ill.[14] Additionally, unlike the 1902 Act, the FDCA explicitly articulated approval criteria for the marketing of drugs; for a drug to be

Regulation, http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm091754.htm ("In 1948, responsibility for biologics rested with the National Institutes of Health, but in 1972, responsibility for biologics control came to FDA.") (last visited Dec. 10, 2009).

[9] The 1902 Act applied to the interstate sale of "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases in man." Biologics Control Act of 1902, Pub. L. No. 57-244, ch. 1378, 32 Stat. 728 (1902).

[10] *See* CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, SCIENCE AND THE REGULATION OF BIOLOGICAL PRODUCTS: FROM A RICH HISTORY TO A CHALLENGING FUTURE 13 (2002), http://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/ProductRegulation/100YearsofBiologicsRegulation/UCM070313.pdf. Note that in 1934 when the NIH promulgated regulations requiring biologic products to be efficacious, the NIH was within the Treasury Department.

[11] Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, ch. 675, 52 Stat. 1040 (1938) (current version at 21 U.S.C. §§ 301-399a (2006)) [hereinafter FDCA of 1938].

[12] FDCA of 1938 § 201.

[13] David L. Stepp, *The History of FDA Regulation of Biotechnology in the Twentieth Century*, 46 FOOD & DRUG L.J. 1, 26 n.80 (Winter 1999), *available at* http://leda.law.harvard.edu/leda/data/257/Stepp,_David_00.pdf (last visited Oct. 9, 2009).

[14] *See* 21 U.S.C. 321 (g)(1)(B) (2009).

approved, it must be shown to be "safe and effective" for use.

In 1944, Congress passed the Public Health Service Act ("PHSA").[15] The PHSA establishes strict standards of safety, purity, and potency that the product must satisfy – standards that continue to govern biologics approval today.[16] The PHSA additionally requires that a manufacturer prove that the facility in which the biologic is manufactured, processed, packed or held meets standards to ensure that the biologic is safe, pure, and potent.[17] Reflecting the complexity of biologics and the importance of manufacturing controls and the manufacturing process, the FDA for many years required that biologics manufacturers submit both a product license application ("PLA") and an establishment license application ("ELA").[18] Only upon approval of both applications was a manufacturer permitted to market the product.[19] The FDA has also required biological products to undergo batch testing and certification prior to the release and sale of each batch.[20] The separate licensing scheme and batch certification historically represented one of the most significant regulatory differences between drugs and biologics.

While most biologics are approved under the PHSA and most drugs are approved under the FDCA, there exist a small number of biologics that have been approved as "drugs" pursuant to the FDCA.[21] In approving some of the first therapeutic biological products manufactured using recombinant technologies, such as human growth hormone, the FDA applied the "safe and

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[15] Public Health Service Act, Pub. L. No. 78-410, ch. 373, 58 Stat. 682 (1944) (codified as amended at 42 U.S.C. §§ 262-300jj (2006)) [hereinafter PHSA].

[16] *See* 21 C.F.R. § 600.3(p)-(s) (2009) (Defining safety as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time;" defining purity as the "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product;" defining potency as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.").

[17] 42 U.S.C. § 262(a)(2)(C) (2006).

[18] Stepp, *supra* note 13 at 28; T. Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L. 77, 84 n.51 (2007)*; see* Public Health Service Act (PHSA) Pub. L. No. 78-410, ch. 373(a) and (d), 58 Stat. 682, 702-703 (July 1, 1944).

[19] Dinh, *supra* note 18, at 84 n.51; *see* Public Health Service Act (PHSA) Pub. L. No. 78-410, ch. 373(a), (d), 58 Stat. 682, 702-703 (July 1, 1944).

[20] 21 C.F.R. § 610.1 (2009).

[21] Jeremiah J. Kelly & Michael David, NO LONGER "IF," BUT "WHEN": THE COMING ABBREVIATED APPROVAL PATHWAY FOR FOLLOW-ON BIOLOGICS, 15 Food & Drug L.J. 115, 116 (2009).

effective", single-license, approval criteria of the FDCA and did not utilize the PHSA.[22] In contrast, for other biologics, such as recombinant human erythropoietin, the FDA relied on the "safe, pure, and potent" criteria of the PHSA (and resulting PLA and ELA requirements).[23] The basis for the determination of which products are primarily regulated under which act is not entirely clear, and, in large part, may rest on the historic approval pathways for the precursor biologic products.[24] When discussing its decision to regulate particular products under the PHSA as opposed to the FDCA, the FDA has also cited the complexity of the products at issue, the PHSA's focus on the manufacturing process, and the enhanced level of oversight that the PHSA allows the FDA (e.g., by allowing immediate license suspension in cases of a public health threat).[25]

In 1997, the Food and Drug Administration Modernization Act ("FDAMA")[26] consolidated the biologic application process and created the

[22] *E.g.* Kathleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 MICH. TELECOMM. TECH. L. REV. 245, 250 (2007), *available at* http://www.mttlr.org/volfourteen/kelleher.pdf.

[23] *See generally* David M. Dudzinski & Aaron S. Kesselheim, *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 New ENG. J. MED. 8, 843 (2008).

[24] For example, hormone and insulin products were approved in their pre-biotech forms under the FDCA, before the FDA gained jurisdiction over biologics in 1972. These products are also not derived from blood and so may not constitute "analogous products" for the purpose of the biologics definition in the PHSA. *See also* Dinh, *supra* note 18, at 83 ("Examples of what constitutes a 'drug' or a 'biological product' will illustrate the confusing logic in FDA's taxonomic system. The classification of some types of compounds is determined by how they are made rather than by what they are or what they do. For instance, 'polynucleotide products . . . are regulated as drugs if they are chemically synthesized, but as biologics if they are biologically synthesized.' On the other hand, the manufacturing method is irrelevant for hormones and antibiotics, which have always been regulated as 'drugs.") (citation omitted).

[25] *See* U.S. Food & Drug Administration, Frequently Asked Questions about Therapeutic Biological Products, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm (last visited Oct. 6, 2009).

[26] Food and Drug Administration Modernization Act, Pub. L. No. 105-115, § 123(f), 111 Stat. 2296 (1997) [hereinafter FDAMA]; *see also* Food and Drug Administration Modernization Act, 64 Fed. Reg. 67,207, 67,210 (Dec. 1, 1999) (to be codified at 21 C.F.R. pts. 314, 601) ("Section 123(f) of FDAMA requires the FDA to take measures to minimize differences in the review and approval of products required to have approved BLA's under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved NDA's under section 505(b)(1) of the act (21 U.S.C. 355(b)(1)).").

Biologic License Application ("BLA").[27] The consolidated BLA permits applicants to submit a single application demonstrating the safety, purity, and potency of a product as well as the integrity of its manufacturing process and facility.[28] Additionally, FDAMA explicitly confirmed the long-held FDA policy of considering biologics as subject to the provisions (aside from approval criteria) of both the FDCA and the PHSA.[29]

B. The Biologics Approval Process

Although the approval processes for drugs and biologics are now functionally similar, important differences remain in the approval criteria: drugs are evaluated against the "safe and effective" standard,[30] while biologics are evaluated against the "safe, pure, and potent" standard.[31] The necessary showing of "safety" and "efficacy" for drugs is well-defined, in that it requires supporting data from at least two "adequate and well-controlled" clinical trials.[32] While the definitions of safety, purity, and potency are found in the biologics regulations,[33] the data required to prove their existence is less clear in that the regulations require simply that an applicant submit "nonclinical laboratory and clinical studies" to support the BLA.[34]

C. The Hatch-Waxman Amendments to the FDCA

In order to understand the FOB debate, it is important to understand the abbreviated application process available for generic drug manufacturers and the related economic incentives for innovative drug manufacturers in the FDCA. In 1984, Congress passed the Hatch-Waxman amendments to the FDCA, creating the generic approval pathway for drugs.[35] Hatch-Waxman

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[27] FDAMA, § 123(a), (f), (g), 111 Stat. at 2323-24 (codified at 42 U.S.C. § 262(a), note to 21 U.S.C. § 355, 42 U.S.C. § 262(j) (2006)); *see also* Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of Biologics License; Elimination of Establishment License and Product License, 64 Fed. Reg. 56,441, 56,443 (Oct. 20, 1999).

[28] 21 C.F.R. § 601.2(a) (2005).

[29] FDAMA, § 123(f), 111 Stat. at 2323.

[30] *Id.* at § 101(1).

[31] *Id.* at § 123(a)(2)(B)(i)(II).

[32] The term "adequate and well-controlled" is also defined in the regulations and generally must consist of trials that are randomized and double-blind. 21 C.F.R. § 314.126 (2008); Hearing Regulations and Regulations Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations, 35 Fed. Reg. 7,250-51 (May 8, 1970).

[33] *See* 21 C.F.R. § 600.3(p)-(s) (2009).

[34] 21 C.F.R. § 601.2(a) (2009).

[35] Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585 (1984)).

established: (1) the approval standards for generic drugs; (2) non-patent exclusivity incentives for innovative and generic manufacturers; and (3) provisions regarding patent disputes between innovative and generic manufacturers.[36] Importantly, biologics were not included under the Hatch-Waxman amendments.

1. Approval Standards for Generic Drugs

Under Hatch-Waxman, a generic drug manufacturer need not conduct human clinical trials to demonstrate that its product is safe and effective.[37] Instead, through filing of an abbreviated new drug application ("ANDA"), the manufacturer may rely on the FDA's findings of safety and effectiveness for the reference drug that the generic product purports to copy.[38] To rely on those findings, the generic drug manufacturer must demonstrate that its proposed product is the same as the reference drug with respect to active ingredient, route of administration, dosage form, dosage strength, labeling, and condition of use.[39] The generic drug must also be bioequivalent to the reference drug, meaning there is no significant difference in the rate and extent of absorption of the active ingredient.[40] If the proposed generic product is not the same as and bioequivalent to the reference drug, there would be no way to assure that the FDA's findings of safety and efficacy for the innovative drug are applicable to the generic drug product.

Importantly, these "sameness" and bioequivalence requirements of Hatch-Waxman are largely inapplicable or irrelevant to biologics. Hatch-Waxman requires that the generic pharmaceutical be identical to the innovator pharmaceutical, a standard that cannot be met for biologics.

2. Incentives for Innovator and Generic Manufacturers

To strike a balance between drug price competition and innovation, the Hatch-Waxman amendments included several provisions intended to reward innovator manufacturers.[41] Distinct from patent protection, reference or innovator product sponsors that receive FDA approval for a new chemical

[36] *Id.*

[37] *Id.* at §101.

[38] *See Id.*

[39] 21 U.S.C. § 355(j)(2)(A)(i)-(v) (2006); *see* H.R. REP. 98-857, pt 1 at 21 (1984) (the purpose of the Hatch-Waxman Act is to ensure that "*the generic drug is the same as the listed drug* that has previously been determined to be safe and effective") (emphasis added).

[40] 21 U.S.C. § 355(j)(8)(B) (2006).

[41] Among these incentives were the patent term restoration provisions. These provisions compensate patent holders for marketing time lost due to product testing and FDA review by extending the length of a patent by a maximum of five years. *See* 35 U.S.C. § 156 (2006); 21 C.F.R. pt. 60 (2009).

entity are provided with 5 years of exclusivity during which the FDA is prohibited from accepting or approving an application for a generic version of the drug.[42] When a reference product sponsor receives approval for a product change such as a new indication or dosage form, it may receive 3 years of exclusivity for the new indication or dosage form so long as clinical trials were necessary to support FDA approval of the change.[43] Hatch-Waxman also provides exclusivity to certain generic manufacturers; the first generic applicant who challenges a listed patent of the reference product sponsor, thereby running the risk of having to defend a patent infringement suit, is eligible for 180 days exclusivity against other generics that challenge the patent.[44] In other words, during the first six months of marketing, no other generic version of the same drug may be brought to market.

3. Patent Provisions

When submitting an ANDA, a generic manufacturer must provide one of four certifications referring to the status of the reference product patents. The most important of these certifications is referred to as a "paragraph IV certification" in which the ANDA applicant represents that a patent for the reference product is invalid, unenforceable, or not infringed.[45] The ANDA applicant who files a paragraph IV certification to a patent must notify the patent owner and the reference product sponsor that it has filed an ANDA containing a patent challenge and must include a detailed statement of the factual and legal basis for the ANDA applicant's opinion that the patent is not valid or will not be infringed. After filing such a statement, the ANDA applicant may be sued for patent infringement. If the reference product holder files a patent infringement suit within 45 days of receiving the notice, the FDA may not give final approval to the ANDA for 30 months from the date of the notice (unless the litigation is resolved sooner).[46] The 30-month bar should in theory allow for resolution of the patent litigation before FDA approval of the generic product. Although Hatch-Waxman did not contemplate an abbreviated approval pathway for biologics, most discussions of FOBs use Hatch-Waxman as a starting point for creating an abbreviated FOB approval process.

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[42] 21 U.S.C. § 355(j)(5)(F) (2006). The FDA may accept an ANDA after 4 years if the pioneer's patent is in dispute. *Id.*

[43] *Id.* However, this 3-year exclusivity has little effect on the innovative product as generics approved for the original indication or dosage form can still be prescribed for such new indications or dosage forms.

[44] 21 U.S.C. § 355(j)(5)(B)(iv) (2006).

[45] 21 U.S.C. § 355(j)(2)(A)(vi)(IV) (2006).

[46] 21 U.S.C. § 355(j)(5)(B)(iii) (2006).

D. Overview of FOB Legislative Proposals Introduced in 2009

As discussed above, Hatch-Waxman represents a highly imperfect model for FOB legislation. Given the nature of biological products and the complexity of the science involved, it has been difficult for lawmakers to reach consensus on approval standards and intellectual property protections for innovators. Generally, the bills pending before Congress would enable a generic manufacturer to submit an Abbreviated Biologics License Application that relies on the FDA's previous findings of safety and effectiveness of the reference product. The bills represent a wide range of opinions regarding the appropriate balance to be struck between the requirements of clinical testing to ensure consumer safety, the incentives available for innovative biotech companies to innovate, and any potential cost savings from the entry of FOBs into biologic markets.

In March 2009, two bills were introduced into the House of Representatives. The bill, the "Promoting Innovation and Access to Life-Saving Medicine Act", was introduced on March 11, 2009, by Representative Waxman along with Representatives Pallone, Deal, and Emerson.[47] This bill would amend sections 351(i) and 351(j) of the Public Health Service Act, add a new section 351(k) to permit licensure of biosimilar biological products, and add a new section 351(l) to provide pediatric exclusivity for biological products. The bill would also amend the Patent Act and Title 28 to address litigation of certain patent disputes prior to FDA licensure of these products. The same bill was introduced into the Senate by Senators Schumer, Brown, Collins, and Martinez. The Waxman bill provides 5 years of data exclusivity for new "major substances," which are not defined in the bill. In addition, the bill provides 3 years for next or subsequent generation product if that product represents a "significant therapeutic advance." The 3 years is not additive to the 5-year base. The Waxman bill would deny exclusivity to products different from, but structurally related to, previously approved products. Up to 6 months of additional data exclusivity is available for a supplement if it is approved in the last year of the exclusivity term, but only if the change represents a "significant therapeutic advance." The Waxman bill would also allow clinical trials to be waived and would establish an inadequate and one-sided approach to addressing patent issues.

On March 17, 2009, Representative Eshoo and 43 co-sponsors (almost 70 as of May 1, 2009) introduced H.R. 1548, entitled the "Pathway for Biosimilars Act."[48] The Eshoo bill provides a base data exclusivity period of 12 years before biosimilar approval, with up to 2 additional years for a new indication

[47] Promoting Innovation & Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. (2009).

[48] Pathway for Biosimilars Act, H.R. 1548, 111th Cong. (2009).

for a potential total of 14 years. A new period of exclusivity is provided for next and subsequent generation biologics. The legislation would allow the FDA to waive clinical trials. The Eshoo bill seeks to establish a more balanced procedure for addressing patents than the Waxman bill.

E. Approval Pathways for FOBs: Required Showing for Biosimilar or Comparable Products

Biosimilar or comparable are the terms generally used to describe how similar the applicant's FOB is to the reference product. The definitions, which generally account for the complexity of biologics manufacture, differ starkly from the "sameness" requirements of Hatch-Waxman. Unlike generics under Hatch-Waxman, which are intended to be identical, FOBs will not be exact copies of innovator products.

1. Data Protection as an Incentive for Innovative Manufacturers

Legislative proposals vary in terms of the duration of new product exclusivity for innovative biologics manufacturers. The Waxman bill provides for 5 years of data exclusivity, though only for new "major substances," a term which is not defined in the bill and which is not a term currently used by the FDA.[49] In addition, the Waxman bill would provide the FDA with explicit authority to identify categories of products that would be entitled to 5 years of exclusivity. The Eshoo bill in contrast would not allow FOBs to be marketed until the later of 12 years after approval of the innovator product or the date that the FDA issues final product class-specific guidance.[50] Both bills limit the degree to which second and subsequent generation biologics – which require a new BLA and are new molecules – would be eligible for data protection. As with Hatch-Waxman exclusivity, the stated intent of these provisions is to provide innovative biologic manufacturers with the opportunity to recoup costs associated with research, development and clinical trials. However, as discussed further below, due to the lack of an appropriate exclusivity provision in the proposed bills and to the potential increased uncertainty of the patent system, R&D investment in this sector may decline, which could have a negative impact on future innovation.

2. Incentives for Innovative Manufacturers: Patent Provisions

The exclusivity provisions of Hatch-Waxman, coupled with various patent protections, are intended to provide innovative manufacturers with a sense of certainty that they will be able to recoup the costs of innovation and product development before facing competition from generic versions of their

[49] H.R. 1427.

[50] H.R. 1548.

products. The approval standards in the legislative proposals threaten this certainty for biologics manufacturers, because they provide for FDA approval of an FOB that is similar – but not identical – to the innovator product. Under such a scenario, FOB manufacturers may be able to obtain approval of a product that is similar enough to rely on the FDA's previous findings of safety and efficacy for the reference product, but different enough to avoid patent infringement.[51] As demonstrated above, while the FOB bills pending in Congress seek to reflect the principles of Hatch-Waxman, the unique aspects of biologics and potential market dynamics should inform the development of an abbreviated regulatory approval pathway for FOBs.

III. BIOLOGICS: KEY SCIENTIFIC AND ECONOMIC ASPECTS

Biologics are highly complex, genetically manipulated proteins produced with living cultures of mammalian, microbial, or yeast cells. Biologics cannot be described in simple terms or using simple formulae because they are the output of a highly complex and nuanced laboratory processes. These fundamental molecular aspects give rise to a host of important clinical, developmental, and economic factors that need to be considered carefully. Biologics produced by the biotech sector are still a relatively new class of drugs. For example, in the early 1980s there were fewer than twenty publicly traded biotech companies in the U.S., with most of them having few or no product sales.[52] Today biologics, which are also developed by traditional pharmaceutical companies, are used for approximately 400 applications and represent some of the most important medical innovations in the past half-century. With the appropriate incentives, it is likely that innovations in biotechnology will continue to revolutionize medicine and perhaps eradicate such illnesses as cancer and heart disease. Science is at the cusp of a new era in genetic research with many promising leads on how human genetics interrelates with disease. For this reason it is particularly important to examine how proposed policy changes will affect R&D investments in the biotech sector. As we discuss in Section IV, the biotechnology industry is fragile in many respects, and new biologic R&D is particularly sensitive to policy and regulatory changes. We turn to some of the details.

A recent study from the Tufts Center for the Study of Drug Development on the cost of developing a new biologic identified several unique aspects of

[51] *See* Bruce S. Manheim, Jr., Patricia Granahan, & Kenneth J. Dow, *'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFF. 394, 398 (2006).

[52] *See* BAYBIO, BIOTECHNOLOGY INDUSTRY MILESTONES, http://www.baybio.org/pdf/BayBio_Biotechnology%20Milestones%20v4.pdf 2 (The first biotech IPO was in 1980.) (last accessed Dec. 10, 2009); Biotechnology Industry Association, U.S. Biotech IPOs, http://www.bio.org/ataglance/bio/200210ipo.asp.

biotechnology R&D.[53] For example, clinical development times for biologics are long because Phase I (the early clinical development stage) is longer than that for small molecule drugs. The overall economic cost of bringing a new biologic to market is estimated to be $1.24 billion, on average (in 2005 dollars). However, the method used in the Tufts Study to measure biologic R&D project risk (necessary for their cost estimate) is likely to underestimate risk (and hence result in a lower cost estimate). This is because the study used the single-factor return model Capital Asset Pricing Model (CAPM) to estimate risk. However, the current most widely-used financial model of risk and return is the three-factor model developed by Fama and French.[54] This is discussed in greater detail below.

Once a new biologic is approved by the FDA for marketing, it faces a product market with different institutional features from most pharmaceutical markets. For example, in contrast to pharmaceuticals, which are typically self-administered, biologics are normally injected or transfused in a clinical setting. This has implications for both companies' product distribution systems and the economic incentives facing the different participants along the healthcare delivery value chain.[55]

Biologic products are also characterized by high fixed costs of establishing scientific and manufacturing capabilities, due to the vast complexities involved in working with living systems and modifying genetic materials.[56] Some researchers have suggested these fixed costs may be 150% higher than the fixed costs associated with manufacturing traditional pharmaceuticals.[57] In one of our own papers, we demonstrate how the future fixed costs of manufacturing facilities lead to higher financial risk (when projects are modeled as real options) because it is equivalent to financial leverage.[58] Large firms may have operational facilities in use that can be adapted or extended, whereas smaller biotech firms are more likely to require a new facility altogether. Thus, investing in biologics entails greater financial risk because of this leverage. This risk would be captured in a three-factor model of risk and return, but not in a single-factor model like the CAPM. These differences in cost structures, time, and financial risk will naturally influence how follow-on

[53] Joseph DiMasi & Henry Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 473-476 (2007).

[54] Eugene Fama & Kenneth French, *Common Risk Factors in the Returns on Stocks & Bonds*, 33 J. FIN. ECON. 56 (1993).

[55] Henry Grabowski, Ian Cockburn, & Genia Long, *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1294-1295 (2006).

[56] Andrew Humphreys, *Difficult Path for Biogenerics*, MEDADNEWS 1 (Dec. 2004).

[57] Henry Grabowski, David Ridley & Kevin Schulman, *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 440, 446 (2007).

[58] Golec, Hegde & Vernon, *supra* note 4.

biologic markets evolve in the U.S.

Follow-on biologics are not likely to be designated as interchangeable by the FDA.[59] The most likely scenario is that they will be treated as therapeutic alternatives by healthcare providers, which will limit their uptake in the market relative to generic pharmaceuticals. Generic pharmaceuticals gain market share very quickly because of mandatory substitution laws. These laws exist in many states and require pharmacists, when presented with a brand-name prescription, to instead dispense the generic version.[60] These laws, and the substitutions they require, make sense where perfect substitutes exist, but follow-on biologics will only be similar to, and never the same as, the original material, and thus not perfect substitutes.

Empirical estimates of the effect that entry has on generic drug prices have been broadly consistent in the traditional pharmaceutical context. For example, one study found that in the case of large selling brand-name products, generic entry and price competition will be swift, with 10 and 20 generic competitors entering and driving prices to marginal production cost within a few months.[61] In fact, generic drug prices in the U.S. are the lowest in the world.[62] But can we expect to observe similar cost savings from follow-on biologic markets? The economic evidence suggests the answer is "no" in the short run.

To begin, relative to the generic pharmaceutical market, there are higher cost-based barriers to entry facing potential follow-on biologic manufacturers. Cell culture facilities require capital investment costs of between $250 and $450 million over three to five years and the costs of pre-market clinical studies needed for approval have been reported to be as much as $40 million in Europe; this is relative to the $1-2 million it costs a generic pharmaceutical manufacturer to demonstrate bioequivalence.[63] In total, it is estimated that follow-on biologics initially will take between five and eight years to reach the market (one to two years of cell biology, a year of process analysis, and between two and four years for pre-market clinical studies).[64] By comparison, a generic pharmaceutical typically requires only a few years to reach the

[59] Grabowski, Cockburn & Long, *supra* note 55, at 1296-97.

[60] RICHARD R. ABOOD, PHARMACY PRACTICE AND THE LAW 132 (5th ed. 2008).

[61] Atanu Saha, et al., *Generic Competition in the U.S. Pharmaceutical Industry*, 13 INT'L J. ECON. BUS. 15, 25-26, 28-29 (2006).

[62] GOODMAN, JC, NATIONAL CENTER FOR POLICY ANALYSIS ANALYSIS, DRUG REIMPORTATION: THE FREE TRADE SOLUTION, Brief No. 503, February 16, 2005, http://www.ncpa.org/pub/ba503.

[63] Grabowski, Cockburn & Long, *supra* note 55, at 1293.

[64] *See generally* Henry Grabowski, Ian Cockburn, & Genia Long, *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFFAIRS 1291, 1293-1295 (2006).

market.[65] When all of these economic factors are taken into account, there are likely to be only a few entrants into even the largest markets for biologics. Price discounts when there are between one and three entrants are estimated to be between 10 and 25%.[66]

IV. FINANCIAL RISK AND BIOTECH R&D

Pharmaceutical and biotechnology R&D is an inherently risky, costly, and uncertain enterprise. Bringing a single new product to market requires huge sums of investor capital and often takes well over a decade.[67] Most R&D projects fail for reasons relating to their safety, efficacy, or commercial viability.[68] Our previous research has shown that firm R&D spending is highly sensitive to both expected returns and financing constraints. In a series of recent papers we have identified a robust empirical link between R&D investment and real drug prices, firm pharmaceutical profit margins, R&D project risk, and the length of a product's market exclusivity period.[69] While all of these studies addressed slightly different issues, and thus had different testable hypotheses, they consistently revealed R&D spending to be highly sensitive to financial returns and risk. This observed relationship was robust to multiple research methods, statistical models, and data samples.

Data exclusivity provisions for biologics and the proposed pathways for follow-on biologics in the current bills are particularly important issues. This is because follow-on biologics will only need to demonstrate a "high degree" of similarity to the brand-name biologic. Thus, the statutory potential exists for follow-on biologics to leverage the abbreviated FDA approval process, in whole or in part, and "design around" the brand-name patent. As discussed in

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[65] Grabowski, Cockburn & Long, *supra* note 55, at 1293.

[66] Grabowski, Ridley & Schulman, *supra* note 57, at 447.

[67] John A. Vernon, Joseph H. Golec, Joseph A. Dimasi, *Drug development costs when financial risk is measured using the Fama-French three-factor model (p n/a)*, HEALTH ECON. (forthcoming), *available at* http://www3.interscience.wiley.com/journal/5749/home.

[68] *Id.*

[69] *See* Thomas Abbott & John Vernon, *The Cost of U.S. Pharmaceutical Price Regulation: A Financial Simulation Model of R&D Decisions*, 28 MANAGERIAL & DECISION ECON. 293, 304-05 (2007); Joseph Golec & John Vernon, *Market Exclusivity and Incentives for Pharmaceutical Investment* (2007) (unpublished working paper, on file with the University of Connecticut Department of Finance) [hereinafter Golec & Vernon, *Market Exclusivity*]; Joseph Golec & John Vernon, *European Pharmaceutical Price Regulation, Firm Profitability, and R&D Spending* (Nat'l Bureau of Econ. Research, Working Paper No. 12,676, 2006); Carmelo Giaccotto, Rexford Santerre, & John Vernon, *Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry*, 48 J.L. & ECON. 195 (2005); John Vernon, *Examining the Link between Price Regulation and Pharmaceutical R&D Investment*, 14 HEALTH ECON. 1 (2005).

the preceding section, the intellectual property rights laws that apply to genetically-altered large molecules are much narrower than they are for pharmaceuticals, due in large part to the minutiae of the cultivation and growth processes involved in manufacturing them. It is therefore easier to "design around" such molecules without encountering patent infringement violations. This artifact of intellectual property rights law places a greater emphasis on data exclusivity provisions for biologic products.

Given that biologics R&D is characterized by high risk, high costs (including the costs and time involved in constructing specialized manufacturing facilities), and substantial uncertainty, as well as substantial dependence on venture and other sources of private capital by smaller firms, an appropriately robust period of data protection is warranted. While it is generally well-known that biotech firms face a high cost of equity capital, previously published analyses have relied on a single-factor return model, the CAPM. This model does not capture two other important types of systematic risk that affect the cost of capital: the size factor and the book-to-market factor. Ignoring these factors when measuring financial risk will underestimate the cost of capital. Moreover, the structural and economic characteristics of firms in the biotech industry make them susceptible to these additional forms of systematic risk. As such, biotech risk will be underestimated when a single factor return model is used. Empirical research has documented this within a large sample of firms in this sector using data going back 20 years.[70] It therefore stands to reason that the innovation incentives needed to ensure continued biotech R&D investment would be higher than the incentives Hatch-Waxman currently provides – incentives that likely are no longer adequate for small molecule drugs. Figure 1 demonstrates this point by considering a hypothetical R&D project and an investment decision as it relates to a product's effective patent life, the project internal rate of return (which increases with effective patent life), and the firm's cost of capital, which is the required rate of return by investors. As Figure 1 shows, holding everything else constant, riskier R&D projects require longer periods of market exclusivity to be judged worthwhile investments from the point of view of investors. This is the well-known risk-return tradeoff. Table 1 presents the same information, but within the context of a net present value (NPV) decision rule for different risk and effective patent length (EPL) periods.

Figure 1: A Hypothetical R&D Project Investment Decision At Two Risk Levels

[70] Golec & Vernon, *Market Exclusivity*, *supra* note 69.

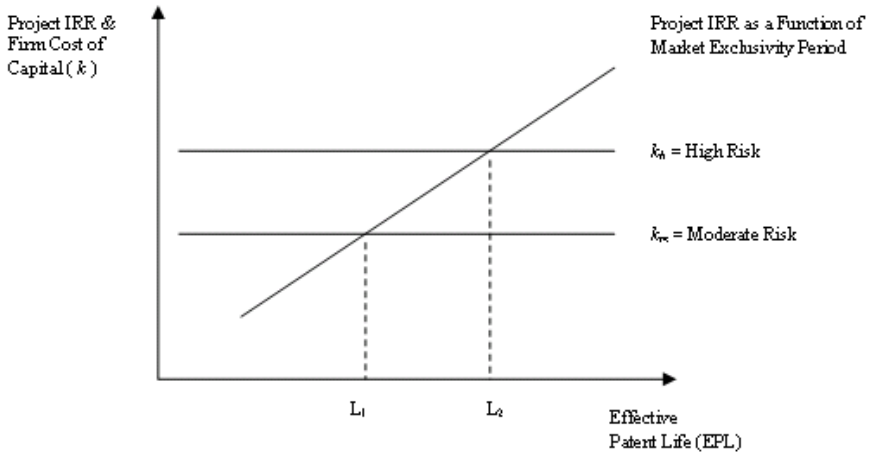


Table I: Simple NPV Decision Rules at Two Risk Levels

Risk Level	EPL < L1	L1 < EPL < L2	L2 < EPL
Moderate	NPV< 0 (No)	NPV>0 (Yes)	NPV>0 (Yes)
High	NPV< 0 (No)	NPV<0 (No)	NPV>0 (Yes)

While it is important to bear in mind that Figure 1 has a number of simplifying assumptions embedded in it, our purpose is only to illustrate that higher risk projects require higher expected rates of return from investors. Thus biologic R&D projects, which often represent a greater financial risk to investors, require stronger intellectual property right provisions than less risky projects when all other considerations are held constant.[71] These risks involve capital market imperfections which are likely to widen the cost of capital gap between biopharmaceutical firms with stable cash flows. Many biotech companies also rely on external capital markets for funding projects. Some of the features unique to firms developing biologics may only be captured within a real options framework, which shows the hypersensitivity of biotech firm stock prices to policy shocks affecting expected future regulations and profits.

[71] One thing that will not be held constant, or be the same, is the competition from generics and follow-on biologics at patent expiration. As discussed, entry in follow-on biologics will not be like it is for pharmaceuticals. This somewhat mitigates the risk premium argument for longer data exclusivity periods relative to brand-name pharmaceuticals.

Without going into any technical detail on this point, the main thrust of argument may be seen and appreciated graphically. Figures 2 and 3 do this by showing both the raw cumulative stock market returns and the risk-adjusted stock market returns for publicly traded firms in the pharmaceutical and biotechnology industries during the period when the Clinton Health Security Act, which contained a plan to use price controls on breakthrough new drugs, was being debated and considered. Although both were affected very significantly, it is apparent that the biotech industry was more adversely affected by this proposed legislation than the pharmaceutical industry.

Examining the raw returns data shows pharmaceutical firms' stocks lost about 32 percent on average, while biotechnology firms' stock lost about twice as much (51 percent). Risk-adjusted returns were much worse: showing losses of 70 and 90 percent, respectively.

One approach to determine the appropriate length of data exclusivity for innovator biologics (which we have argued necessarily must exceed the market exclusivity period for small molecule drugs of 11 to 12.5 years) is to combine our previous research[72] on the cost of capital for biotechnology R&D using the Fama-French model[73] (nominal 16.25% or 12.75% real based upon a 3.5% rate of inflation) with the cash flow analysis research undertaken and published by Grabowski.[74] Grabowski's research determined that the requisite data exclusivity periods for innovator biologics lies between 12.9 and 16.2 years.[75] He based his analysis on an 11.5% and 12.5% real cost of capital range (from earlier studies of the cost of capital in the pharmaceutical industry using the CAPM).[76] As discussed previously, biologics R&D involves a high degree of financial risk. Thus, Grabowski's upper limit estimate of 16.2 years is slightly low. A first approximation extrapolation from his results suggests the appropriate length of data exclusivity should be closer to 17 years.

Figures 2 and 3: Stock Price Reactions to a Policy Shock: Pharma vs. Biotech[77]

[72] Golec & Vernon, *Financial Risk*, *supra* note 1, at 19-23.

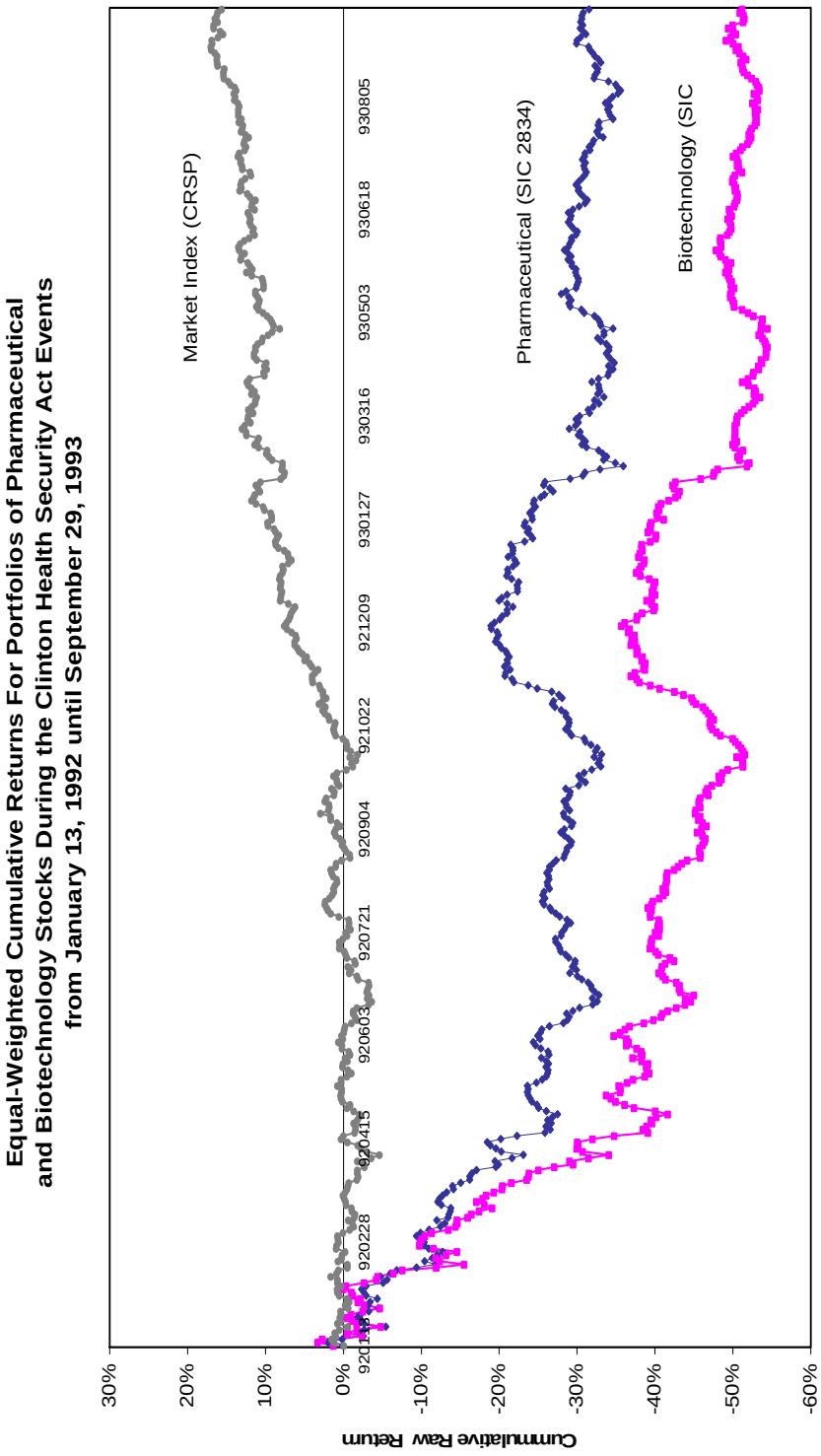
[73] *See* Fama & French, *supra* note 54.

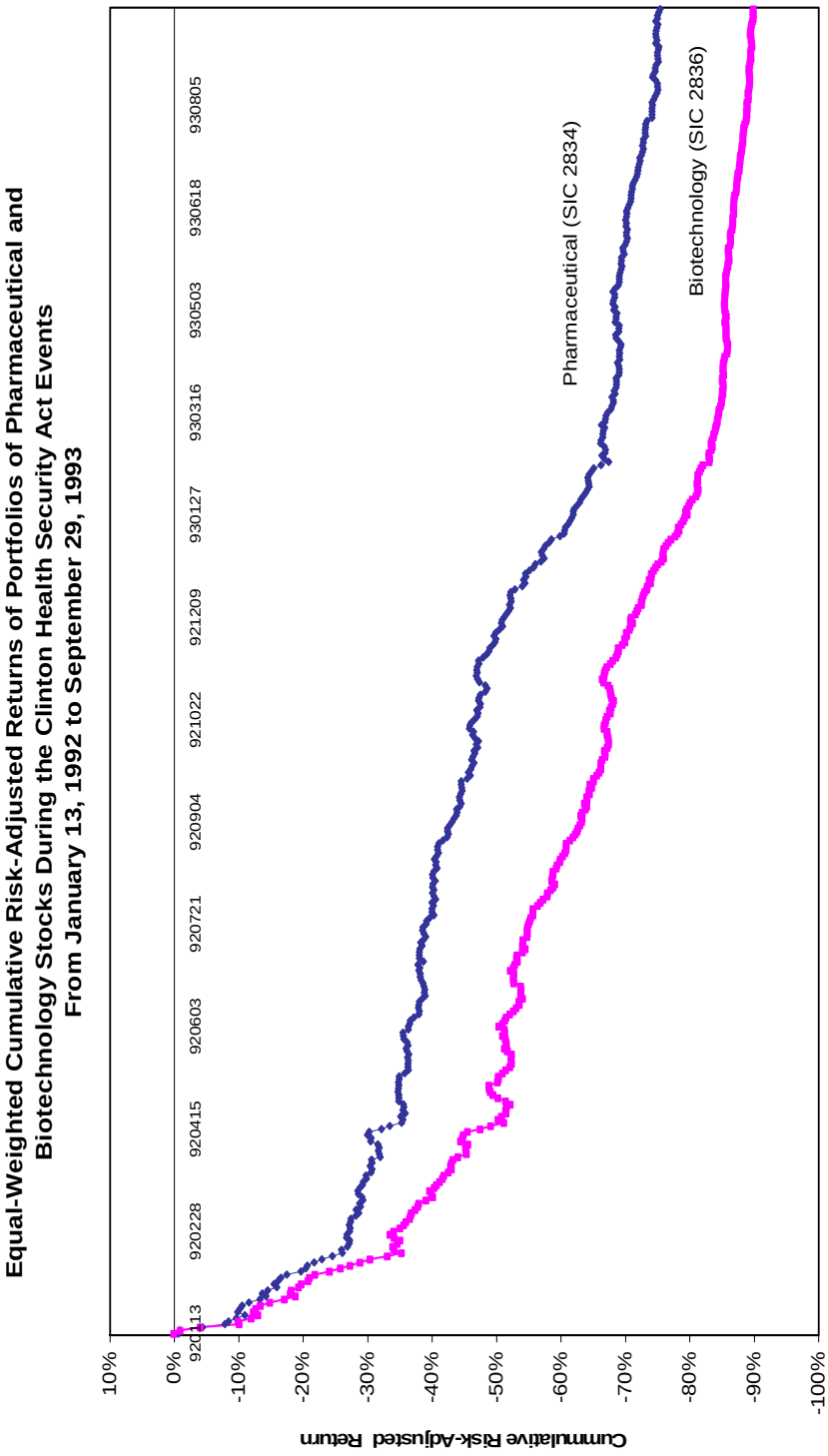
[74] *See*, Grabowski, *supra* note 6.

[75] *Id.*

[76] *Id.*

[77] Joseph Golec, Shantaram Hegde & John Vernon, *Pharmaceutical Stock Price Reactions to Price Constraint Threats and Firm-Level R&D Spending*, (Nat'l Bureau of Econ. Research, Working Paper No. 11229, 2005) (forthcoming in the Journal of Financial and Quantitative Analysis).





As a final consideration, we note that in some of our previous research we estimated the elasticity of firm R&D spending with respect to effective patent life, measured at the industry level, to be approximately unit elastic.[78] This implies that a 10 percent increase (decrease) in effective patent life increases (decreases) firm R&D spending by 10 percent as well. Given that research suggests that the U.S. is currently under-investing in medical and pharmaceutical R&D (given the measured social benefits of these activities), an understanding of how the length of data exclusivity for biologics impacts incentives for R&D is warranted; indeed, it is necessary for sound policy formulation.[79]

V. CONCLUSIONS

As Congress considers legislation to develop an abbreviated regulatory approval pathway for FOBs, one of the most critical aspects to consider is how best to ensure continued incentives for innovation, and the tremendous medical advances they promise. As this research suggests, a minimum of 17 years of data exclusivity or data protection is required to provide the necessary incentives for continued biotech R&D investments. The high-risk and uncertain nature of biotech R&D has been underscored by the effects of the economic downturn on the biotech sector. A majority of biotech companies had a market cap well below $100 million and at the end of 2008, almost 90% of firms remained unprofitable.[80] Furthermore, evidence suggests that these incentives are in fact inadequate for pharmaceuticals in light of the social rate of return to both pharmaceutical and medical R&D.[81] This analysis suggests that the U.S. is under-investing in these areas. One study suggests that for every $1,345 invested in pharmaceutical R&D, a U.S. life year is gained, on the average.[82] The standard valuation of a life year in the U.S. is in the range of $100,000 to approximately $175,000.[83] It may be an opportune time to take a closer look at the direction of healthcare policy in the U.S. and the property

[78] *See generally* John A. Vernon, Joseph H. Golec, Randall Lutter, & Clark Nardinelli, *An Exploratory Study of FDA New Drug Approval Times, Prescription Drug User Fees, and R&D Spending*, 49 Q. REV. ECON. & FIN. 4, 1260 (2009).

[79] *See, e.g.*, MEASURING THE GAINS FROM MEDICAL RESEARCH, *supra* note 7, at 206-248.

[80] Burrill & Co., *Biotech's Small Cap Companies Restructuring to Save Cash* (Dec. 1, 2008), *available at* http://www.burrillandco.com/news-331.html; Eun K. Yang, et al., Jefferies & Co., *Cash Is King: Where Biotech Stands* (Oct. 15, 2008).

[81] MEASURING THE GAINS FROM MEDICAL RESEARCH, *supra* note 7, at 206-248; Lichtenberg, *supra* note 5, at 15-18.

[82] Lichtenberg, *supra* note 5, tbl. 3.

[83] MEASURING THE GAINS FROM MEDICAL RESEARCH, *supra* note 7, at 17; David Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20 HEALTH AFF. 11, 13 (Sept./Oct. 2001), *available at* http://content.healthaffairs.org/cgi/reprint/20/5/11.pdf.

right provisions for pharmaceuticals and biologics.