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ON BEHALF OF

THE
BIOTECHNOLOGY INDUSTRY ORGANIZATION

ON

Biologics and Biosimilars: Balancing Incentives for Innovation

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Subcommittee on Courts

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(December 22, 2008) (available at http://www.econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf)

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I. Overview

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide the views of its members on intellectual property issues implicated by an abbreviated regulatory procedure for the approval of highly similar biological products, or so-called "biosimilars."

BIO supports the creation of an abbreviated pathway for biosimilars to help increase competition among, and access to, the many breakthrough biomedical advancements that have been developed by the biotechnology industry over the past 25 years. In doing so, providing effective intellectual property protection for biological products must remain a central focus of Congressional efforts. Measures that operate to lessen the economic incentives of our current system will translate into fewer new biological products and therapies, to the detriment of patients with currently unmet medical needs.

Patents are an important component of these economic incentives. Patents protect the inventions that are made throughout the process of discovering and developing a new biological product. For example, our members use patents to protect not only the protein that is the heart of a new biological product, but new treatments based on that product, new formulations necessary to make the product viable, and a wide range of techniques and systems used to produce, test, evaluate and use these products. Our companies also rely on trade secrets to protect manufacturing know-how and a range of data generated during the extensive and expensive process of clinical testing of a new biological product or treatment.

The effectiveness of the intellectual property incentives that exist today for encouraging development of new biological products and therapies, however, is inextricably linked to the regulatory system that governs these biological products.

Today, any company wishing to market a biological product must independently prove that its product is safe, pure and potent. This means that each company wishing to bring a new biological product to market must conduct the same scale of clinical testing for its product, and face the same risks, costs and other barriers to market, whether the product is highly similar to an existing product or an entirely new molecule. This level playing field among competitors directly influences decisions an innovator makes to undertake new product development, and continue clinical development of biological products after they have been approved. It also has functioned to blunt the impact of the limits of patent protection available for biotechnology products imposed by current law and strict examination standards used by the U.S. Patent and Trademark Office (PTO).

An abbreviated regulatory pathway for approving biological products will fundamentally change this environment. By its very design, an abbreviated approval process leverages the investments and efforts of the earlier innovator to facilitate approval and market entry of a biosimilar product that will directly compete with the innovator product. By allowing the biosimilar manufacturer to "free-ride" on the clinical data of the innovator, the abbreviated pathway helps the biosimilar manufacturer bring its product to market faster, with far less risk and uncertainty, and at a fraction of the innovator's development costs.

Unquestionably, the business of biotechnology innovation will change once an abbreviated pathway for biosimilar products becomes available. And patent rights, as they exist in today's system, simply will not be sufficient to preserve the incentives for development of new biological products and treatments that exist in today's industry. Measures that offset the impact of these fundamental changes to the nature of competition in today's biotechnology industry must be integrated into any new regulatory approval system for biosimilar products.

With these points in mind, BIO believes three principles must be followed in shaping any new abbreviated biosimilar approval process.

First, a substantial period of data exclusivity must be provided for the companies that conduct the clinical testing necessary to bring a new biological product, or a new use of biological product, to market. The certainty delivered by a lengthy period of data exclusivity is essential to preserve the dynamic economic environment essential to the viability of this industry and to continue to foster its entrepreneurial, innovation-focused and high risk-taking character. It is also necessary to offset the limits of patent protection that are presently mitigated by high barriers to entry facing other innovator products, but which will not be present once an abbreviated pathway for biosimilars is available.

In this regard, BIO strongly supports the data exclusivity provisions in H.R. 1548 introduced by Representative Anna Eshoo (D-CA) and supported by a broad bipartisan coalition of more than 125 Members of the House of Representatives, along with a wide range of stakeholders, including the American Association of Universities, the National Venture Capital Association, and scores of patient advocacy groups. This bill provides a base period of 12 years of protection, with the possibility of up to two and a half more years for conducting additional clinical research for new indications and pediatric populations.

Alternative proposals that provide no or only short periods of data exclusivity – or rely solely on the patent system – ignore the obvious and substantial changes to the biotechnology business model that will occur with the creation of an abbreviated approval pathway. These proposals also ignore the fact that patents will play a very different role in these systems as compared to how they operate today for generic drugs under the Hatch-Waxman Act. Specifically,

under the regulatory system that governs approval of small molecule drugs, innovators do not see competition from generic products for 12 – 14 years after the innovator product was launched, as a result of the combination of innovator patents, patent term restoration and data exclusivity provided for new molecules and new indications of drug products.

The critical distinction that makes this model break down for biological products is that biosimilar products will not be required to have an active ingredient that is the same as the active ingredient in the innovator's product, given the impossibility, with today's science, to make an exact copy of a biologic. Rather, they require differing degrees of "similarity." Indeed, some of the legislative proposals in this area would permit abbreviated approval of a biosimilar with significant differences in molecular structure, mechanism of action, and manufacturing processes. The lack of a "sameness" requirement will create significant questions about whether patents that cover an innovator's product will also cover a potential biosimilar product. The possibility exists that they will enable biosimilar manufacturers to achieve something generic drug manufacturers cannot, namely, avoid the innovator's patent rights but still get the benefit of the innovator's clinical data. A substantially longer period of data exclusivity than that provided to small molecule innovators in today's generic drug approval system is thus needed to preserve the incentives for innovation and clinical development of biological products.

Second, any legislation must include a balanced and fair procedure for identifying and resolving patent disputes implicated by the structure of a biosimilar product and how it is made *before* the biosimilar product is approved and put on the market. Nearly all stakeholders agree that doing so is better for patients, caregivers, and both innovator and biosimilar companies. To be fair and effective,

the system must permit participation by all relevant biotech stakeholders – including the universities and small biotech companies that have a significant role in our industry – and must not artificially skew the way that patent litigation is conducted to favor one party or the other. Indeed, doing so would likely run afoul of our international trade commitments, because they would make use of biotechnology patents less effective and useful compared to patents in other fields of technology.

In this respect, BIO strongly opposes statutory provisions, such as those found in H.R. 1427, the biosimilar legislation introduced by Representative Henry Waxman (D-CA), that would operate to arbitrarily limit the number of relevant patents that could be litigated prior to biosimilar approval, that would give one but not the other party control over whether, where and how litigation is conducted, or that impose onerous sanctions on the patent owner to enforce administrative compliance with the system. Measures that disrupt the well-settled rules of civil procedure and evidence and limit judicial autonomy will invariably make litigation more complex, more unpredictable and produce unfair results – directly contrary to the goals this Committee has had for years in its efforts to enact patent reform. BIO supports the patent notification and litigation procedures in H.R. 1548 because they do not suffer from these problems and will provide a fair and straightforward process for expeditiously identifying and resolving patent issues implicated by a biosimilar product

Third, any legislation should provide regulatory linkage to encourage innovator companies to promptly raise and resolve patent issues. Regulatory linkage, which is integral to the Hatch-Waxman Act, provides that, if a patent owner establishes through litigation that its patent is valid and infringed, the Food and Drug Administration (FDA) will defer granting final approval to the generic

application until the infringed patent expires. BIO believes a similar regulatory linkage must be integrated into any new analog to the Hatch-Waxman system created for biosimilar products to ensure that valid patent rights are respected. In this respect, we support the regulatory linkage provisions of the Eshoo bill, and regret that this measure has been excluded from H.R. 1427.

BIO also wishes to bring to the Subcommittee's attention a number of serious concerns it has with the recent report of the Federal Trade Commission (FTC) on intellectual property issues and biologics. BIO firmly believes the FTC's recommendations on data protection and patents are grounded on a number of serious errors and omissions, and reflects opinions that are contrary to decades of experience within our industry. If adopted, the FTC recommendations would seriously erode the incentives for development of new biological products.

II. Background on BIO and the Biotechnology Industry

BIO represents more than 1,200 companies, universities and research institutions that use biotechnology to research and develop cutting-edge healthcare, agricultural, industrial and environmental products and applications. As of December 31, 2008, there were more than 1,700 biotechnology companies established and doing business in the United States, 371 of which were publicly held, having an aggregate market capitalization of over $340 billion. The biotechnology industry and its contribution to U.S. economic growth has mushroomed since 1992, with U.S. healthcare biotech revenues increasing from $8 billion in 1992 to $70.1 billion in 2008. U.S. employment in the biosciences reached 1.3 million in 2006, and this industry indirectly supports approximately 6.2 million U.S. jobs Biotechnology companies can be found in every State of the Union. Roughly 80 percent of BIO's corporate members are small businesses.

The biotechnology industry is one of the most research-intensive industries in the world. In 2008 alone, biotechnology companies spent more than $30 billion in R&D. Between 2003 and 2007, the biotechnology industry raised more than $100 billion in private investment. These investments are paying off. There are more than 200 new drug products and vaccines on the market and hundreds more in development. These products are now improving, and will continue to improve, the lives of millions of Americans, and offer hope for cures for a wide range of illnesses.

The key to success of the biotechnology industry – across all of its sectors – is a business model that is based on taking significant risks to develop products based on innovation. Specifically, the biotechnology business model is based on making significant investments (often hundreds of millions of dollars) in early stage research and development with the hope that some of these investments and efforts will yield a commercial product. This model has worked despite the fact that it is lengthy (often taking more than a decade) and that the vast majority of biotechnology R&D investments and efforts do not result in a commercial product reaching the market. It is only by pushing boundaries of science and taking these risks that breakthrough inventions are discovered and converted into commercially viable products and services.

The biotechnology business model requires an environment that, as much as possible, reduces unpredictability in the commercial sector. One important factor in this environment is the guarantee of data exclusivity and effective patent protection. Specifically, by ensuring that the products or services that may eventually be marketed can be protected from unauthorized copying and use, companies can justify taking risks and making significant R&D investments. Introducing greater unpredictability by inadequate periods of data exclusivity, or

by limiting the conditions in which patent rights can be asserted, will adversely affect the business environment that is so crucial to supporting innovation in the biotechnology sector. And reducing this uncertainty has, time and again, proven to be critical to the decision-making processes of those providing funding for this research and development, particularly the venture capital community.

II. Key Concepts Involved in Biosimilar Legislation

A. Data Exclusivity

In the ongoing biosimilars debate, what "data exclusivity" is and what its effects will be have been misconstrued and often obfuscated. Misleading terms such as "marketing exclusivity" or "branded exclusivity" have been used interchangeably with this term; indeed, data exclusivity has even been characterized as a "monopoly" right. Given its central importance to the debate, it is important to have a clear understanding of what data exclusivity is, and what it can and cannot do within an abbreviated regulatory approval pathway.

An abbreviated regulatory approval procedure for biosimilar products will be able to provide a substantially faster, more certain and vastly less expensive regulatory approval process by allowing the biosimilar manufacturer to rely, at least in part, on the clinical evidence produced by an innovator and used to support FDA approval of the innovator's product (often called the "reference" product). In this type of an approval system, "data exclusivity" refers to a period of time after the approval of the innovator product during which the FDA is not allowed to rely on the approval of the innovator's product, including data contained in the innovator's Biologics License Application (BLA), to support approval of the

biosimilar product. Data exclusivity will prevent "unfair commercial use" of clinical test data, which often cost hundreds of millions of dollars to generate.[1]

Data exclusivity is provided today under the Federal Food, Drug and Cosmetic Act (FDCA) for small molecule pharmaceutical products.[2] In that system, a certain amount of time must elapse (between five and seven and one half years) before the FDA can approve a marketing application by a drug applicant who, instead of doing its own clinical trials, wants to rely on clinical studies that were done by another for an earlier drug. If the generic applicant does not want to wait until the "data exclusivity" period expires, it can generate and submit its own safety and efficacy data at any time.

This deferral of FDA reliance on the innovator's clinical data plainly is not an innovator "marketing exclusivity" or a "monopoly" right. Any competitor can submit independently generated clinical safety and efficacy data for its product at any time and receive FDA approval. Indeed, data exclusivity gives no innovator the right to monopolize the market for a new drug molecule, and current experiences in the biotechnology industry prove the contrary, as the FTC report

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1 Data exclusivity provisions are found in the regulatory systems of most developed countries. Data protection independent of trade secret protection is also required by international agreements, such as the Agreement on Trade Related Aspects of Intellectual Property (TRIPS). *See* TRIPS Agreement, Article 39.3.

2 Under U.S. law, data exclusivity is also provided for agricultural chemical products. In that system, the producer of a "generic" pesticide must wait at least ten years before it can rely on the EPA's approval of the innovator pesticide. *See* Federal Insecticide Fungal and Rodenticide Act (FIFRA), 7 U.S.C. § 136a(c)(1)(F)(i) and (ii). This ten-year data exclusivity period for pesticides is supplemented by compensation paid by the "generic" manufacturer to the innovator for the five years following the end of the innovator's exclusivity period. *See* 7 U.S.C. § 136a(c)(1)(F)(iii).

amply demonstrates.[3] Terms such as "monopoly" or "marketing exclusivity" simply should be eliminated from the biosimilars debate.

Under the FDCA, the timelines for FDA action also apply regardless of patent status. For example, if an innovator obtains FDA approval of a new molecule, the FDA can accept and approve a competitor's application based on independently generated clinical evidence for the same molecule at any time, regardless of who owns the patent (or regardless of whether the molecule is patented at all). If the competitor wants to rely on the innovator's safety and efficacy data, however, the FDA will not accept an application for a copy of that molecule for four to five years from the innovator's approval date – again, irrespective of who owns the patent, if any.[4] Data exclusivity thus operates independently of patents. Also, unlike patents, data exclusivity is not enforceable by one private party against another, and there is no mechanism under which an innovator can sue a competitor for violating its data exclusivity.

Although data exclusivity does not confer marketing exclusivity or monopoly power, it does play a very important role in incentivizing innovation and in protecting investments – a role also commonly associated with patents. But in doing so, data exclusivity operates in a very different, but complementary, manner to patent exclusivity. For example, a drug applicant that seeks FDA approval based on an earlier drug's clinical safety and efficacy data, but does not infringe any patent could be deemed a free-rider of the innovator's investment in clinical

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[3] For example, seven different human growth hormone products have been introduced and compete in the U.S. market. *See* FTC Report at 21-22.

[4] An applicant may submit an abbreviated new drug application ("ANDA") four years after approval of the NDA if it contains a patent certification under § 505(j)(2)(A)(vii)(IV) asserting that one or more patents listed for the drug product are invalid or would not be infringed by the ANDA product. *See* FDCA § 505(c)(3)(E)(ii). If there are no patents listed for the drug, or if the ANDA applicant does not intend to challenge any listed patents, the ANDA may be filed on the date that is five years after the approval of the innovator's NDA.

research, but not a patent infringer. By contrast, a drug applicant that has made large investments in clinical research and seeks FDA approval of a molecule patented by another but on the basis of its independently generated clinical evidence could be deemed a patent infringer, but not a free-rider.

Both scenarios occur regularly today. To avoid patent infringement, the applicant would have to design around the patent and make something other than a copy of the patented molecule. To not "free-ride", the applicant would have to conduct its own clinical research instead of relying on a competitor's clinical research. Data exclusivity thus will prevent free-riding on investments in clinical research that are necessary to secure marketing approval of a biological product, while patents operate to prevent unauthorized use or copying of innovative technology, each for a limited time. And, because copying and free-riding are both toxic to the initial and continued development and clinical testing of innovative biologics and therapies, both of these complementary and independent mechanisms are necessary, especially when one recognizes that the risk of patent avoidance and patent design-arounds will inherently be a much more significant problem for biologics, as explained below, than it is under the Hatch-Waxman Act framework for generic drugs.

Currently, there is no authority for the FDA to rely upon the clinical data a biologics manufacturer has provided to the agency in its BLA to support approval of any other biological product.[5] This means that, today, any company that wishes

[5] As is the case with the abbreviated new drug approval procedures for small molecule drugs under § 505(j) of the Federal Food, Drug and Cosmetic Act, any authority given to the FDA to rely on the innovator's BLA to justify approval of a later biosimilar application would not authorize the FDA to publish or share any confidential, trade secret information contained in the BLA. *See* FDA Response to Citizen Petition Docket Nos. 2001P-0323 *et al*. at fn 14 (Oct. 14, 2003). Instead, like the § 505(j) authority, it would grant FDA a limited authority to "use" that information to support its decision to find the biosimilar product pure, potent and

to obtain approval for a biological product, including one that is highly similar to an innovator product, must independently generate its own clinical data and convince the FDA on the basis of that data that its new product is pure, potent and safe. The average cost of doing this, as has been well-documented, is enormous, exceeding $1.2 billion.[6]

Today's biotechnology development environment thus imposes a substantial economic barrier to entry for new biological products, including those that are the similar to, or function similarly to, existing biological products. Indeed, this feature of the industry is *why* a substantial period of data exclusivity is essential to any future system for approval of biosimilar products. Decisions made by innovator companies today are based not only on the assumption that some degree of patent protection will be available to protect the innovator product in the future, but that every other potential direct competitor will face similar risks of failure, costs of conducting clinical investigations, and the same scientific uncertainties that the innovator faced. These factors have operated, in practice, to encourage not only the extremely high-risk initial development effort, but also the continued clinical research to find new uses for the product once it has been initially approved.

The availability of an abbreviated approval process for biosimilar products will fundamentally change this economic equation for innovators. Data exclusivity, and more specifically the length of data exclusivity, will become critical. As numerous experts have explained, a substantial data exclusivity period will be required to, in essence, "recreate" the dynamic and competitive

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safe in the absence of independently generated clinical data and reports establishing the safety, potency or purity of the biosimilar product.

6 *See*, *e.g.*, Joseph A. DiMasi and Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?* 28 MANAG. DEC. ECON. 469, 470 (2007).

environment that exists today and is so critical to driving initial and continued clinical investigation and development of drugs and new indications.[7]

A substantial data exclusivity period is particularly critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and where research and development needed for early-stage or adjuvant cancer therapies, which are more difficult and take longer, generally occur later. The substantial exclusivity provided for the original treatment will encourage and support the risky, complex and expensive further development of the product for these additional indications, and will be critical to bring to market the vibrant pipeline of treatments that can allow cancer patients to live longer and better lives.

Importantly, data exclusivity periods will run concurrently (not in addition to) any patent exclusivity that may exist for the innovator's product, which may last up to or beyond 14 years after approval of that product. In one sense, a 14-year data exclusivity period will serve as an insurance policy that provides the innovator with certainty of protection for this period. In the case of patents that cannot be designed around and that have significant amounts of patent term remaining, long data exclusivity will have no impact. On the other hand, a substantial data exclusivity period becomes relevant where the available patent term is short, or where the biosimilar was designed to be different enough to avoid that patent but similar enough for approval. A substantial period of data exclusivity thus is an essential component of a balanced statutory pathway for biosimilars, making possible their introduction and use in the market while appropriately safeguarding incentives for biotechnology innovation.

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[7] *See*, *e.g.*, Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503-570.

BIO accordingly supports the data exclusivity provisions found in H.R. 1548. Under H.R. 1548, a new biological product would enjoy a base period of 12 years of data exclusivity, meaning that no biosimilar application could be approved that references the innovator's BLA earlier than 12 years after the BLA was approved. H.R. 1548 provides incentives for encouraging continued clinical research on an innovator biological product by providing that the base period can be extended by two additional years if the product is subsequently approved for a significant new indication. It also encourages pediatric testing of biologics, by providing the possibility of an additional six-month period of exclusivity. These periods are cumulative, so that an innovator product could enjoy a period of up to 14.5 years measured from the original approval of the product.[8] BIO believes both the structure and the periods of data exclusivity provided by H.R. 1548 reflect a fair balance, and will help to preserve the incentives existing under our current system to drive both original research and development of new biological products, and to stimulate continued clinical development of existing products to address new and unmet medical needs.

B. Patent Protection

A patent provides its owner with the right to prevent others from making, using, selling, offering for sale or importing the patented invention.[9] Patents are granted by the PTO following an examination process during which a patent examiner evaluates whether the invention is new, useful, non-obvious and

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[8] Some have argued that this bill and others like it would permit innovators to make minor changes to their products and receive additional, successive 12-year periods of data exclusivity. This is incorrect. The bill's express language makes clear that the date of "first licensure," which starts the 12-year data exclusivity clock, cannot be extended by changes to a product's dosage, strength, or route of administration, and provides only a single, two-year extension for any new indication approved for the biological product.

[9] 35 U.S.C. § 154.

adequately described and enabled in the patent application.[10] Patent claims – which define the boundaries of protection conferred by the patent – are evaluated, and ordinarily narrowed, during the examination process to correspond to what the PTO believes represents the patentable invention. The exclusive rights under a patent are enforced through litigation in a Federal district court, which is an expensive, resource-intensive and often unpredictable process.

Over the past 15 years, the legal standards governing patentability of biotechnology inventions, and how the PTO applies them, have become significantly more stringent. For example, the utility requirement under 35 U.S.C. §101[11] and the written description requirement under 35 U.S.C. § 112, first paragraph,[12] have been construed by courts and the PTO to require more information about the nature and implications of changes to a protein or nucleic acid structure to justify the grant of patent claims extending beyond the literal protein sequence that has been discovered. *See*, *e.g.*, *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005); *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). At the same time, the courts and the PTO have tightened the requirements for a finding of

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[10] 35 U.S.C. §§ 102, 103, and 112.

[11] In 1995, and again in 2001, the PTO issued guidelines relating to the "utility" standard of 35 U.S.C. §101. *See*, *e.g.*, *Utility Examination Guidelines,* 66 Fed.Reg. 1092 (Jan. 5, 2001). Under these guidelines, the PTO has demanded applicants identify a specific, substantial and credible utility for their inventions. The PTO has supplemented these guidelines with training materials that illustrate how to apply the standards properly. *See* **http://www.uspto.gov/web/offices/pac/dapp/mpep_examguide.html**.

[12] In 2001, the PTO issued guidelines on application of the "written description" requirement of 35 U.S.C. §112, first paragraph. *See Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement*, 66 Fed. Reg. 1099 (2001). As applied by the PTO, the guidelines require applicants to provide a comprehensive written description of what they perceive their invention to be as of the filing date of the patent. Again, the PTO followed the guidelines with training materials that provide examples of commonly encountered scenarios, with clear guidance on when to impose rejections. *See* **http://www.uspto.gov/web/offices/pac/dapp/mpep_examguide.html**.

"non-obviousness" of an invention – a measure of whether the pre-existing knowledge in the prior art makes an invention "obvious" or not – under 35 U.S.C. § 103.[13] The effect of these changes in law and examination practice has made it increasingly difficult to emerge from the examination process with claims that grant broad rights beyond the specific protein sequence that was tested and evaluated before the original patent application was filed, or slight variations relative to that sequence.[14]

Biotechnology patents must be pursued promptly after an invention is made. If an inventor waits to file the application, and the research becomes public, it can prevent the patenting of the invention, both within and outside the United States. This pressure to file early, however, creates a tension with the potential commercial value of the patent, as patent rights can only be used, as a practical matter, after FDA approval of the innovator's product or an infringing biological product. In other words, given that the term of a patent runs 20 years from the original filing date of the patent, and that it can take 12 to 15 years to obtain marketing approval for a new biological product, the resulting period of "effective" term remaining after the BLA for the biological product is approved thus can be quite short.

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[13] *See*, *e.g.*, *KSR Int'l. Co. v. Teleflex Inc*., 550 U.S. 398 (2007); *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009); *Leapfrog Enter., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157 (Fed. Cir. 2007).

[14] Patents claiming proteins or nucleic acids often employ a concept of "homology" relative to a specified sequence. For example, a patent may claim all proteins having an amino acid sequence that is 99% homologous to a specified sequence. The PTO has issued extensive guidance to its examiners and the public regarding evaluation of "homology claims" during the examination process. *See, e.g.*, PTO Written Description Guideline Training Materials, Revision 1 (March 25, 2008), available at **http://www.uspto.gov/web/menu/written.pdf**; PTO Revised Interim Utility Guidelines Training Materials, available at **http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf**.

Moreover, as part of the Hatch-Waxman Act package in 1984, Congress statutorily exempted from infringement any activities conducted by the developer of a new drug or biological product that are reasonably related to obtaining FDA approval of the product.[15] This means that the owner of a patent covering an infringing drug or biological product cannot stop infringements arising solely from the FDA approval-related activities of a biosimilar manufacturer.

Recognizing both of these factors, Congress, as part of the original Hatch-Waxman package, provided these patent owners with a way to restore lost "effective" patent term caused by the requirement for pre-market regulatory review. The patent term extension provisions permit a patent owner to recover up to five years of effective patent life, subject to several limitations. First, the overall effective patent term after the extension cannot exceed 14 years, regardless of how long the regulatory review of the product took. Second, only the initial approval of a biological product can serve as the basis for restoration. Third, the rights granted by the extension are limited to those that correspond to the approved product. And, finally, only one patent may be extended on the basis of a regulatory review period, and no patent may be extended more than once.[16]

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[15] Congress exempted from infringement those acts that are reasonably related to obtaining approval of a new drug, biological product or medical device. *See* 35 U.S.C. § 271 (providing that "It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention … solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."); *see also Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005).

[16] The limitations of the existing patent term restoration authority under 35 U.S.C. § 156 raise a number of questions concerning biological products. For example, biotech companies often obtain, using special accelerated approval procedures, a first approval of a new biological product for a relatively narrow indication that affects fewer, but desperately ill patients. This first approval, however, by statute, serves as the basis of any restoration period request. Thus, a company that conducts substantially longer, more complex and more expensive clinical investigations for the primary indication of a biological product cannot secure a patent term restoration corresponding to the much longer regulatory review period required

The parameters of the patent term restoration provisions of the Hatch-Waxman Act in 1984 reflect Congress' determination that an effective patent term of 14 years following approval of the product is an appropriate period of patent exclusivity.[17] In enacting these provisions, Congress acknowledged that – unlike most other industries – the pharmaceutical industry rarely benefited from the full length of the standard patent term (then 17 years from grant of the patent) due to the long development and regulatory approval process for drugs. Given that Congress has previously concluded that 14 years of patent protection is appropriate for drugs and biological products, any statutory formula that allows for biosimilars should at least guarantee that same degree of effective market protection – and, for the reasons discussed above, that protection can be accomplished most predictably through data exclusivity.

C. Patents Alone Cannot Provide the Incentives Necessary to Encourage Today's Level of Innovation and Clinical Development of Biological Products in a New Biosimilar Approval System

Reliance on the patent system alone in a future system including a biosimilar pathway will prove insufficient to stimulate the scale of continued innovation and clinical development of biologic products that exists in today's system. A "patents only" approach also ignores past and ongoing changes in patent law and the

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for that primary indication. Patent term restoration rights are also limited to the rights in the "product." Some have questioned whether the patent term restoration rights would cover a biosimilar product that has a different molecular structure relative to the innovator product. Revisions to these provisions of 35 U.S.C. § 156 to preserve the intended functioning of the patent term restoration authority, or to permit greater latitude for biotech companies to select the basis of the extension, may be warranted incidental to review of a new follow-on biologics ("FOB") approval system.

[17] Extension is calculated by taking: ½ of the time spent diligently from the investigational new drug application effective date to new drug application ("NDA") submission; and the full NDA review period; patents cannot be extended by more than five years. The patent extension also cannot result in a patent that has a term of more than 14 years post-NDA approval.

fundamental changes to the biotechnology business model that would be implemented by an abbreviated approval pathway, and that patents and regulatory standards will interplay very differently under a biosimilar pathway compared to how they operate today under the Hatch-Waxman framework for generic small molecule drugs.

Under the 1984 Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, a generic version of a small molecule drug may be approved for marketing only if its active ingredient is the "same" as the innovator product.[18] Thus, any patents that cover the innovator's drug molecule necessarily apply to the duplicate, generic version, and a generic may not enter the market until the innovator's patent expires. Indeed, the manufacturer of a generic drug may not have it both ways – it cannot gain FDA approval of its product by demonstrating that the active ingredient is the same as the innovator product and then turn around and claim in the patent context that it is different.

Overall, the robust framework of patents, data exclusivity, and stringent generic drug approval standards under the Hatch-Waxman Act has resulted in a dynamic, innovation-driven and highly competitive market for small molecule drugs. In this market, through this combination of measures, innovator small molecule drugs enjoy substantial periods before generic competition commences. The Congressional Budget Office found that the average period of time for marketing of a drug product with patent protection before generic competition begins is 11.5 years,[19] and new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.[20]

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[18] FDCA § 505(j); FDA, Critical Path Opportunities for Generic Drugs (May 2007)

[19] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter

Under the statutory framework being considered for biosimilars, the same array of measures will not consistently produce equivalent periods for innovator biological products. Unlike a small molecule generic drug, a biosimilar will not be required to be the "same" as the innovator product. Instead, it will only have to be "similar" or "highly similar" to the innovator product. While the meaning of this standard may vary between legislative proposals, there is no question that it falls short of the degree of sameness required of generic drugs relative to their pioneer reference products. In fact, under some current legislative proposals, the requirements for similarity are defined in a way that would allow for approval of biosimilars with significantly different structures or other differences relative to the innovator product.

As a result, under these proposed approval schemes, a biosimilar product will frequently achieve what has been expressly prevented by the design of the Hatch-Waxman Act; namely, a finding that the biosimilar product is "sufficiently similar" to the innovator biologic to justify reliance on the safety and effectiveness of the innovator's clinical evidence (and thereby secure expedited approval of the biosimilar product), yet sufficiently "different" to avoid patent infringement. This paradox will permit a biosimilar product to bypass the mechanisms that Congress has designed to encourage innovation and investments in clinical development of the innovator product, and to thereby get on the market well in advance of innovator patent expiration at a fraction of the innovator's development costs.

Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation." A more recent study found that this period is actually closer to 13 years. *See* Charles Clift, *The value of patent term extensions to the pharmaceutical industry in the USA*, 5 J. GEN. MED. 201 (2008).

[20] Henry G. Grabowski and Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, MANAGERIAL AND DECISION ECONOMICS (*forthcoming)*.

The impact of a less stringent "similarity" approval standard is compounded by the fact that patent claims on biologics must often be narrowly drawn to the specific innovative aspect (*e.g.*, a specific protein or nucleotide sequence) to be allowable. The unpredictability inherent in the biological products, in particular, leads to stringent applications of the patent law standards of utility, written description and enablement.[21] In turn, this prevents issuance of broad "genus" claims that cover a wide range of structural variations to the particular protein sequence discovered and tested by the innovator.[22] By contrast, a group of structurally related bioactive molecules (a so-called genus) that are the basis of most NDA drugs can often be covered by a single patent claim.[23]

Due to a series of court decisions, the patent law is leading inexorably to even narrower patent claims. While this trend impacts all inventions, it has especially significant consequences for protecting innovator biologics in a new biosimilar regime. Developments that lead to narrower patent claims for biological products and how they are made will create wider gaps that may enable a biosimilar to exploit the innovator's investments in clinical development and

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[21] *See*, *e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051 (Fed. Cir. 2003); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

[22] The "utility," "written description," and "enablement" requirements of the Patent Act are interpreted more stringently for biotechnology inventions than for most other technologies. Moreover, patents cannot claim something that occurs naturally. Because many biotech products are "artificial" (recombinant) versions of naturally occurring proteins, the patent claims must be narrowly crafted (*i.e.*, limited to specific isolated and purified DNA sequences, proteins, or clonal cell lines) in order to avoid encompassing naturally produced molecules. In contrast, most of the small medicinal molecules are synthetic, and because they these molecules were not pre-existing in nature, broader claims can be secured covering a range of structurally similar molecules.

[23] The active ingredient identity requirements in the FDCA approval procedures for generic drugs also lessens the necessity of broad "genus" patent protection in conflicts between an innovator and a generic drug manufacturer.

thereby receive regulatory approval while still eluding the innovator's patents.[24] Furthermore, the sheer size of biologic products – often several hundred- or thousand-fold larger than small molecule drugs – increases the number of possible ways of altering the product such that it would be similar enough to the original product to qualify as "biosimilar" but different enough to be outside the scope of the patents on the original product. Disputes over patent claim coverage that are likely to arise from this situation would lead to an increase in litigation expenses and add to the uncertainty that biotechnology companies face.

Because of differences in available patent protection and less stringent biosimilar approval standards, the mix of robust patents and data exclusivity periods currently provided to small molecule drugs will prove incapable of preserving the incentives necessary for discovery and clinical development of biologic products that exist today in the biotechnology industry. Instead, significantly longer data exclusivity periods are needed to offset this patent uncertainty and preserve the balance that Congress found necessary to stimulate innovation in the small molecule pharmaceutical industry.

In crafting a biosimilars regime, it is especially important to err on the side of incentivizing innovation due to the unique elements of the biotechnology industry, which is largely comprised of small, unprofitable, privately-funded start-up companies without reliable revenue streams. These companies are heavily dependent on private capital to support their research and development activities. They must bear not only the enormous costs and high degree of uncertainty of their product development, but must make the case that they should be given, over and

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[24] Bruce S. Manheim, Patricia Granahan, and Kenneth J. Dow. *'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry*, HEALTH AFFAIRS (March/April 2006).

over again, additional investments of private capital they need to continue their innovative research and development work. Thus, compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to factors that make securing investments more difficult, particularly those that could result from a poorly-crafted biosimilars regime.

III. Addressing Issues Concerning Effective Data Protection and Patent Protection Measures in Biosimilar Legislation

BIO supports the establishment of an appropriately balanced system for approval of biosimilar products. Of course, the devil is in the details. Intellectual property issues that must be resolved include the duration and structure of data exclusivity provisions, and the availability and nature of measures to resolve patent disputes prior to approval of the biosimilar product.

A. BIO Positions on Pending Legislation Concerning Biosimilar Approval Procedures

The two bills pending before the House (H.R. 1548 and H.R. 1427) reflect highly divergent perspectives on data protection and procedures for addressing patent conflicts.

1. BIO Strongly Supports the Data Exclusivity and Patent Provisions in H.R. 1548

As noted earlier, the data exclusivity measures in H.R. 1548 will provide an effective structure for and duration of data exclusivity for innovators. BIO strongly supports both the structure and duration of data exclusivity that would be provided under H.R. 1548 for innovator biological products. BIO believes those provisions will provide strong incentives to conduct both the original development of a new biological product, and to continue clinical research to extend use of the biological product to address additional unmet medical needs of patients.

H.R. 1548 also would establish balanced and inclusive measures concerning patents implicated by a biosimilar product. Significant features of this system, which BIO supports, include:

- A procedure that enables the BLA holder and third-party patent owners to identify relevant patents based on information provided by the biosimilar applicant under appropriate conditions of confidentiality.[25] This structure will permit small biotech companies and universities to participate in pre-marketing patent identification procedures, and will not require these entities to have their interests represented exclusively by the BLA holder. This makes sense, given that in many instances patents implicated by the biosimilar product will not be assigned to or subject to the control of the BLA holder.

- A requirement for the biosimilar applicant to take a position, as is done in the Hatch-Waxman Act, on each patent that has been identified which expires after the end of the data exclusivity period for the innovator's product. The biosimilar applicant must either request the FDA to defer grant of final approval until the expiration of a particular relevant patent, or assert that the patent is invalid or not infringed. Like the Hatch-Waxman Act, doing this creates the artificial act of infringement necessary to provide standing for suit, in light of the §271(e) exemption, which exempts activity done to generate information for FDA review from infringement.

- A requirement that a patent owner commence suit within 60 days of receiving a certification adverse to the patent by the biosimilar. It also preserves the ability of a biosimilar applicant to commence a declaratory judgment action at an appropriate time during this process

[25] The FTC incorrectly suggests that requirement is unprecedented, and could lead to anticompetitive conduct. *See* Fed. Trade Comm'n, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (June 2009) at p. 57-59, *available at* www.ftc.gov/os/2009/06/P083901biologicsreport.pdf. In reality, patent owners routinely obtain this type of information from patent defendants in litigation, subject to the terms of a protective order issued by a court. Moreover, current law already provides analogous procedures. Under the Hatch-Waxman Act, a generic drug applicant may make an offer of confidential access of its ANDA to the NDA holder during the 45-day period where the NDA holder must commence suit under any listed patents that the generic has challenged. *See, e.g.*, FDCA § 505(j)(5)(C)(i)(III). The provisions of H.R. 1548 simply parallel these routine practices followed in litigation and under the Hatch-Waxman Act.

to resolve questions about any patents, which the patent owner has not asserted but in respect of which the biosimilar applicant made a certification.

- A regulatory linkage provision directing the FDA to defer approval of the biosimilar application until the date a patent found to be valid and infringed expires, provided that the district court does so prior to the date that the data exclusivity in the product has ended.

Notably, H.R. 1548 does not include a provision imposing an administrative deferral of approval of a biosimilar application during the pendency of the patent litigation, as is done in the Hatch-Waxman Act. Instead, it provides a powerful incentive for patent owners to conclude the litigation as rapidly as possible. This incentive provides regulatory linkage for those entities that obtain a district court ruling on the patent prior to the expiration of the data exclusivity period. The structure of this provision will encourage the parties, particularly the patent owner, to promptly conclude the litigation. In addition, the structure of these provisions, which provides that the FDA will be able to grant final approval to the biosimilar application at the expiration of the data exclusivity period of the innovator, will ensure that ongoing patent litigation will not affect the timing of FDA final action on biosimilar applications.

H.R. 1548 also does not contain measures that unfairly sanction patent owners who do not comply with administrative procedures relating to patent notification, or that unfairly tilt the litigation process in favor of one party at the expense of the other. Instead, under the structure of the bill, a patent owner that does not accurately identify patents or timely participate in the notification process concerning identified patents will not be able to secure regulatory linkage for those patents. The bill thus preserves the autonomy of the courts to manage litigation, and does not attempt to change well-established rules governing civil procedure, evidence and venue.

2. BIO Opposes the Data Exclusivity and Patent Provisions in H.R. 1427

The data protection provisions in H.R. 1427, in contrast to those in H.R. 1548, are extremely limited in duration and subject to conditional eligibility and post-approval developments. These measures will not provide effective incentives for initial development and approval of a new biological product or for the continued development of new indications of biological products. Indeed, under the bill's provisions, only those products that are "not similar" to existing products could receive any period of data exclusivity. Plainly, these provisions will not provide the certainty and clarity that biological innovators require *before* they commence the risky, expensive and difficult process of discovering and clinically developing a new biological product or treatment.

The patent provisions in H.R. 1427 are similarly unbalanced and will prove ineffective in achieving the goal of identifying and promptly resolving patent disputes prior to approval and launch of a biosimilar product. These provisions would inappropriately limit and distort the standards governing venue and standing in patent disputes, and impose harsh punitive sanctions on patent owners – including on patents expressly excluded from the patent notification procedures – to enforce compliance with administrative measures governing notice about patents. These administrative sanctions, would statutorily limit the exclusive rights conferred by the patent in unprecedented ways in American patent law. For example, a patent owner who attempted to timely comply with the administrative notification process, but failed, would be foreclosed from obtaining injunctive relief and would have its patent remedies limited to recovery of a reasonable royalty regardless of the actual harm caused by the infringement. The sanctions for administrative errors that would lead to a failure to identify a relevant patent –

whether owned by the BLA holder or not – would result in a sanction that would entirely foreclose use of the patent against any infringer.[26]

These curtailments of the patent property right are unprecedented in American patent law and reflect an overt bias against the use of legitimate, constitutionally mandated patent rights. They also will operate to make biotechnology patents less effective in preventing the unauthorized use of the inventions that these patents are supposed to protect, which will run afoul of U.S. commitments under the WTO Agreement on Trade Related Aspects of Intellectual Property (TRIPS). In particular, Article 27.1 of TRIPS prohibits discrimination in the availability and enjoyment of patents rights based on the field of technology of the invention. If these measures pass, they would single out biotechnology patents only for limitations that undoubtedly alter the capacity of these patents to prevent unauthorized use of the protected technology, and thus run afoul of this important international standard.

H.R. 1427 also provides no incentives for patent owners to participate in the scheme that has been designed, including, critically, no regulatory linkage for the successful assertion of a patent against a biosimilar applicant. Instead, the bill expressly provides that the FDA is to approve the biosimilar application regardless of whether patent litigation has been commenced or concluded. Designing a process, which, on the one hand, acknowledges that valid patents may be infringed by a biosimilar product, yet, on the other hand, actually makes it harder to enforce or use those patent rights, provides no incentive for patent owners to expeditiously

[26] H.R. 1427 takes the unprecedented step of entirely nullifying the patent property right to enforce the administrative notification provisions of the bill. Specifically, the bill proposes to add to the patent statute new §271(e)(6)(C), which would provide that "the owner or licensee of a patent that should have been disclosed [under the notification process of the bill] but that was not timely disclosed … may not bring an action under this title for infringement of the patent."

conclude litigation, nor does it remove uncertainty over the status of the biosimilar product in light of these valid patents.

B. The FTC Has Made Radical Proposals Not Supported by Evidence or 30 Years of Experience of the Biotechnology Industry

The FTC, in its recent report on intellectual property issues in biologics, has missed an opportunity to constructively advance the legislative discussions about intellectual property issues in a new biosimilar approval pathway. Instead, it has staked out radical positions that ignore the substantial experience of industry and the extensive economic evidence about development of biological products that was provided to the Commission. In addition, several of its critical assumptions rest on serious errors about the nature of biotech patent rights and the operation of data exclusivity provisions.

The FTC reached two conclusions following its solicitation of public input: (i) no period of data exclusivity can be justified by the FTC's understanding of the economics of the biotechnology industry, and (ii) no procedure should be provided to permit early resolution of patent conflicts before the actual commercial launch of a biosimilar product. In essence, the FTC takes the position that the nature of competition between innovator and biosimilar manufacturers in the future will be identical in character and effect as that which exists today between innovative biological producers. As a result, the FTC concludes that no changes are needed to accommodate what nearly all commentators recognized will be a fundamentally different competitive landscape in the biotechnology industry.

BIO believes adopting legislation based on the FTC's flawed and unsound theories will fundamentally erode the incentives for developing new biological

products, for conducting clinical research to bring these products to market, and expanding their use to new indications.

1. The FTC Has Incorrectly Portrayed the Nature and Effects of Competition between Biosimilar and Innovator Companies

BIO recognizes that the nature of competition between an innovator and biosimilar producer in the future will not be the same as that which exists today between small molecule pioneer drug manufacturers and generic drug companies. For example, the requirement that the biosimilar producer conduct some amount of clinical investigations on its product, the higher overall costs and greater complexity of producing biological products, and critically, the lack of a current scientific basis for treating the biosimilar product as being interchangeable with the pioneer biologic, all will contribute to greater barriers to market entry for biosimilar manufacturers than those faced by generic drug manufacturers. Biosimilar manufacturers also will likely have to engage in some amount of marketing and promotion of their products, in addition to leveraging the lower costs of producing them, to achieve significant market penetration relative to generic drug products.[27]

The FTC, however, flips this point on its head, concluding that, because the nature of competition between innovator and biosimilar manufacturers will not be the same as that between innovator and generic drug manufacturers, somehow this means there will be no economic impact of an abbreviated biosimilar pathway

[27] Once patent and data exclusivity expires in a pioneer small molecule drug, conversion of the market to generic versions of the drug is essentially automatic. *See, e.g.*, http://energycommerce.house.gov/Press_110/110-ltr.050208.respto040308.FTC.pdf (observing that as a result of the policies of public and private health plans and state substitution laws, generic manufacturers typically capture anywhere from 44 to 80 percent of branded sales within the first full year after launch of lower-priced generic products).

sufficient to justify creating any new incentive measures for biotech innovator companies. The FTC makes several fundamental errors in reaching this conclusion.

The first, critical error the FTC makes is to equate the nature of future competition between biosimilar and innovator manufacturers with the competition that exists today between only innovator companies. In reality, there will be a fundamentally different type of competition in the future when a biosimilar pathway is established. Indeed, to conclude otherwise, the FTC must assume the central objective of creating a biosimilar pathway (*i.e.*, to substantially decrease the costs, risks and uncertainty of bringing a competing biological product to market) will fail. In other words, despite acknowledging that a biosimilar pathway will create an entirely new form of competition within the biotechnology industry, and will undoubtedly have a negative impact on the market of innovator companies, the FTC somehow concludes that no new incentives of any kind should be included in the new regime to preserve today's incentives for biotechnology innovators.

The FTC also incorrectly assumes that patents alone are the means by which innovator companies justify their decisions to develop new biological products and treatments. They are not. Central to the decision of a biotech company to undertake development of a new biological product, or to continue clinical development of an existing product, is assessing the risk of a competitor developing a competing product. That risk today is defined in terms of an environment where every company faces the same level of risks and costs of development. Patents cannot today, and will not in the future, provide certainty regarding competition with these products.

Simply put, the picture created by the economic risks that first innovators see in today's market from competition from other innovators has no relevance to the picture they will see when a biosimilar approval pathway exists. Indeed, virtually no industry outside of pharmaceuticals does the government permit wholesale "free riding" on the investments of the first innovator to market, much less encourages it to promote price competition. How the FTC concludes that that there will be no impact on innovation from this fundamental change to the nature of competition within the biotechnology industry is simply baffling.

The FTC also phrases its question in a way that is destined to lead to the wrong answer. The question is not whether Congress should enact provisions that delay entry and restrict competition – of course, Congress should not. The proper question is what measures must Congress include in a system designed to facilitate creation of a fundamentally new type of competition in the biotechnology industry (*i.e.*, between biosimilar and innovator biologics manufacturers) without substantially diminishing today's incentives for innovators to invent, develop and bring new biological products and treatments to market, for the benefit of patients. The answer, provided by rigorous, peer reviewed economic research, is a substantial period of 12 to 14 years of data exclusivity. Nothing other than conjecture supports the FTC's unfounded assertions.

2. The FTC Incorrectly Describes the Capacity of Patent Rights Alone to Encourage Initial and Ongoing Clinical Research in a Biosimilar Market

As noted above, while patent rights can be secured to protect biotechnology products, these patent rights tend to be narrow and centered on the specific product and features of the innovator biological product. A biotech company, or an investor considering supporting that company, evaluates the risk that these narrow

patents will not block competition by structurally similar biological products by assuming that few, if any, of those products will reach the market, and they will do so only after the first product has enjoyed a substantial period of commercial success. The considerable market barriers in today's *innovator-only* market thus operate to offset the risks created by these narrow or uncertain patent rights. If substantial data exclusivity provisions are not included in a future biosimilar approval system, there will be no "offset" to these patent risks.

There is no question that biotechnology companies assert their patents against competitors today to prevent the unauthorized use of the protected technology, and will do so in the future against biosimilar manufacturers. However, the capacity of these patents to prevent unauthorized use of the innovator's technology is uncertain. And it is this uncertainty, coupled with a fundamentally different form of competition that a biosimilar approval pathway will create, that demands additional measures to incentivize innovation, particularly data exclusivity. The FTC's conclusions to the contrary are based on its incorrect assumptions about the scope and effectiveness of biotechnology patents.

First, the FTC asserts that patent claims can be secured today that cover proteins or nucleic acid sequences that vary up to 30% relative to the innovator's product, asserting that "an FOB drug product's molecule could differ by up to 30 percent and still infringe the patent protecting the pioneer product."[28] In patent claim terms, this is a claim that would cover a polypeptide or nucleic acid sequence that is "70% homologous" to a reference sequence.

[28] *See* FTC Report at 36-37, citing Chris Holman, 17 ALB. J.SCI & TECH, 1, 44 (2007).

The FTC is simply wrong in asserting that the PTO routinely grants patent claims conferring this breadth of protection. Importantly, the FTC does not provide any analysis from its sister agency, the PTO, about the PTO's actual practices in granting patents on protein or nucleic acid sequences to support these assertions. It also undertook no independent analysis of issued patents, whether historical or under current practices, and elected to ignore the extensive evidence provided by patent practitioners about their current experiences with PTO practices concerning "sequence homology" claims. This is surprising, given how important the FTC's assumption of effective patent protection being available is to its conclusion that no new measures will be needed to preserve incentives for biotechnology innovation once a biosimilar pathway has been established.[29]

What the evidence shows is that the PTO historically has taken a very conservative stance on "homology" claim breadth. Indeed, the PTO, particularly after adoption of more stringent written description and utility standards in 2000, demands extensive evidence from applicants to justify protein or nucleic acid "genus" claims. Under these examination practices, claims are usually limited to the specific protein or nucleic acid sequence discovered by the inventor, or at best cover a narrow range of variants – usually proteins or nucleic acids that are 95% to 98% identical to the reference sequence.

This description of actual experiences before the PTO was clearly communicated by nearly every patent practitioner who participated in the FTC's hearings and public notice process. Inexplicably, the FTC not only chose to ignore this evidence, but relied on it being incorrect to justify a central assumption of its

[29] The PTO maintains a special office, the Patent Technology Monitoring Team (PTMT), to assist other agencies and the public in obtaining information on patenting trends and practices. The PTMT conducts analysis and publishes reports on patents, and patenting trends; *See* http://www.uspto.gov/web/offices/ac/ido/oeip/taf/tafp.html.

paper; namely, that broad patent protection is available now, will be available in the future, and will enable innovators to prevent the unauthorized marketing of biosimilar products for decades to come.

The FTC similarly dismissed arguments from experienced patent litigators who identified challenges in using protein or nucleic acid sequence claims to prevent unauthorized marketing of biosimilar proteins. Instead, the FTC reviewed outcomes from litigation involving patents issued in the late 1980s and early 1990s, which did not employ "homology" limitations, and generally did not involve relevant (if any) questions of infringement.[30] Somehow it concluded "biotechnology drug product claims have been construed so that accused products have been found to infringe even when they have varied from the patentee's corresponding product."

Actual experience in litigating protein or nucleic acid patent claims refutes this central assumption of the FTC, and shows that substantial challenges do exist to proving infringement of a sequence claim even where the changes of the infringing product are relative minor.[31] The FTC thus compounded its errors about the nature of claims being issued *today* – which will be the only patents relevant in

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[30] FTC Report at 37. Examples of cases the FTC cites to support its assertion include *Genentech, Inc. v. Chiron*, 112 F.3d 495 (Fed. Cir. 1997), which did not involve a question of infringement, but concerned the scope of claims involved in an interference proceeding; *Amgen v. Chugai* 927 F.2d 1200 (Fed. Cir. 1991), concerning a patent issued in 1987 (*i.e.*, long before current written description and utility standards) and in which infringement was not a central issue.

[31] *See Hormone Res. Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558 (Fed. Cir. 1990); *Novo Nordisk of North America, Inc. v. Genentech, Inc.*, 77 F.3d 1364 (Fed. Cir. 1996); *Genentech, Inc. v. Wellcome Found. Ltd.,* 29 F.3d 1555 (Fed. Cir. 1994); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003); *Biogen, Inc. v. Berlex Labs., Inc.*, 318 F.3d 1132 (Fed. Cir. 2003); *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094 (Fed. Cir. 2003). These cases illustrate that courts have indeed sometimes taken a very a narrow view of biotechnology patent claims, under which even very 'close' products were determined not to infringe a valid patent.

future patent litigation concerning biosimilar products – by citing irrelevant cases and ignoring numerous decisions that illustrate the challenges and uncertainty of proving infringement of proteins having even minor variations relative to a claimed protein or nucleic acid sequence.[32] Current PTO practices and experiences from past litigation thus show, contrary to this critical FTC assumption about patent certainty and effectiveness, that substantial challenges will be encountered by innovators attempting to use homology patent claims to prevent market entry by structurally distinct biosimilar products.

3. Preventing Enforcement of Patents until after Marketing of a Biosimilar Product Begins Will Cause Undesirable Confusion in the Market and Undermine Patent Rights

Nearly all stakeholders in the biosimilar debates support inclusion of procedures to identify and resolve patent issues before a biosimilar is approved and placed on the market. The reasons are simple; patent litigation commenced only after the biosimilar product is launched will lead to a longer period of uncertainty about patents and will cause greater market disruptions concerning the biosimilar product. Providing a way to start patent litigation before the biosimilar product is on the market (*i.e.*, during the data exclusivity period of the innovator and while the biosimilar product cannot be marketed because it is undergoing review by the FDA) will benefit patients, physicians, insurers, follow-on manufacturers and innovators alike. Indeed, without such a mechanism, follow-on products will enter the market under a cloud of patent uncertainty, and, once on the market, patent

[32] The FTC also entirely ignored the challenges of proving infringement under the "doctrine of equivalents" under current law, where a claim amendment made before the PTO to narrow a homology claim will create substantial obstacles to securing relief against a protein or nucleic acid sequence that lies outside the literal scope of the patent claim. *See*, *e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002).

disputes over such products will not allow patients, physicians, and insurers to assume there will be long-term availability of the biosimilar product.

Congress has recognized the benefits of starting litigation to resolve patent disputes before generic drugs enter the market. In 1984, as part of the Hatch-Waxman Act, it created special procedures for starting patent litigation before generic small molecule drugs are approved. Under this system, patent owners identify patents that are relevant to its drug. Due to the "sameness" requirement integral to generic drug approval, those patents will be relevant to any generic version of the innovator's drug. Generic drug applicants then must take a position on those "listed" patents; either wait until they expire, or identify specific reasons why the patents are invalid or would not be infringed by the generic product. If the generic applicant challenges a listed patent, the patent owner may promptly commence suit, and litigate the patent. While this litigation is ongoing, the FDA will not grant final approval to the generic drug application, provided that litigation is concluded within 30 months of the generic drug providing notice about the patents. If the patent owner ultimately prevails, demonstrating its patent is valid and infringed by the generic drug, the FDA will defer the final approval of the generic drug application until the expiration of the infringed patent.

The patent resolution provisions established by the Hatch-Waxman Act have generally served their intended purpose of reducing uncertainty for innovators and generics alike, which helps explain why there is broad support among stakeholders for inclusion of similar procedures in a future abbreviated biosimilar approval system. Despite this broad support, the FTC argues that a pre-marketing approval patent litigation procedure should not be provided in a future biosimilar approval system. Like its other recommendations, this recommendation is based on flawed assumptions about patent litigation and the broader public interest.

One justification the FTC provides for its position is its conclusion that the rapid market erosion following generic drug entry with small molecule drugs will not occur following the launch of a biosimilar product.[33] The Commission relies on this assumption of slow market erosion to assert, in essence, that patent owners will have plenty of time to litigate their patents while the biosimilar product is on the market before significant economic harm is caused to the innovator. This argument ignores the impact of patent uncertainty around the continued marketing and availability of the biosimilar product, the principle justification that has led most stakeholders to call for a pre-launch patent procedure. It also rests on shaky economic and market behavior assumptions that only the FTC has advanced.[34]

The FTC also somehow manages to conclude that patent owners will be able to effectively enforce their patents without any new procedures, attempting to analogize innovator-biosimilar patent disputes to those between biotech innovator companies, or between patent owners and infringers in other industries. The Agency's attempt to analogize biosimilar-innovator litigation to past litigation between biotech innovator companies is based on a flawed understanding of the circumstances of those cases,[35] and ignores the economic symmetry that existed

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[33] *See* FTC Report at 52-53.

[34] The FTC data minimizes the potential market impact, based on early information from biosimilar experiences and the 10-year scoring window used by most studies. The FTC uses this same argument to support the notion that patent design arounds, even if they occur, will not harm innovators sufficiently to support the need for data exclusivity. For the same reasons, that analysis is likewise flawed.

[35] The FTC mischaracterizes past cases involving biotech innovators, incorrectly suggesting that this litigation occurs only after the infringing product has been approved by the FDA. *See* FTC Report at 54 ("By contrast, if litigation were to begin post-approval, the way in which branded biologic competitors resolve patent issues currently, …"). In reality, most of the cases cited by the FTC involved situations where the product accused of infringement had not been approved at the time of the litigation. *See, e.g.*, *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) (neither Amgen nor Chugai product approved at time of litigation); *Amgen Inc*. *v. Hoffmann-LaRoche Ltd*., 2008 U.S. Dist. LEXIS 77343 (D. Mass 2008) (accused product not approved at time of litigation).

between these innovator litigants, which will not exist in litigation between innovator and biosimilar manufacturers. The FTC also ignores the high frequency of patent settlements in biotech cases, which reveals the value innovator companies place on patent certainty after having made significant investments in product development. And, critically, the FTC fails to acknowledge that forcing patent disputes to commence only after a biosimilar has been placed on the market will undermine the value of patent exclusivity, because it will raise the prospect that a court will not enforce the exclusive rights of the patent by issuing an injunction preventing the continued marketing of the biosimilar, even if the patent is found valid and infringed.

The FTC's attempt to analogize innovator-biosimilar litigation to experiences of patent owners in other industries is similarly based on flawed understandings. Two significant factors differentiate innovator-biosimilar litigation from litigation in other industries. First, the Bolar exemption prevents many innovator and biosimilar manufacturers from litigating patent disputes where the biosimilar's pre-approval activities are reasonably related to securing FDA approval for the biosimilar product, and thus are exempt from patent infringement. No such restraint is placed on patent owners in other industries, meaning that a patent owner can commence litigation to enforce its patent rights as soon as a patent owner becomes aware of the infringer's plans to commence marketing an infringing product. Second, other industries do not operate within a statutory scheme that is designed to encourage copying of the innovator's product and free-riding on the innovator's immense pre-market investments. And, the market disruption following removal of an infringing feature from a non-medicinal product, such as a consumer electronics product, cannot be compared to removal from the market of a biosimilar product.

The FTC also claims that a pre-approval patent notice and litigation procedure will be unlikely to succeed in providing patent certainty, citing a variety of theories.

- It asserts that innovators with "vulnerable" patents will benefit from a system where these patents will only have to be litigated after the biosimilar is approved, reasoning, in essence, that these "vulnerable" patents would not be invalidated or held not infringed as early as they would under a pre-approval challenge process.[36] What this hypothetical actually demonstrates is that biotech innovators need a substantial period of data exclusivity to offset risks of inadequate patent estates.

- The FTC appears to believe that a patent owner will have different incentives in pre- vs. post-approval patent litigation, suggesting that only in the latter will patent owners assert their "strongest" patents.[37] In reality, biotech companies will have equal incentives in both situations to select those patents that will deliver the best outcome in the litigation.

- The FTC observes that an early start to patent litigation "does not guarantee that patent issues will be resolved earlier…" citing the possibility that new patents will issue after the litigation starts or even after the biosimilar is approved.[38] The FTC is wrong in a very important respect. An earlier commencement of litigation will help resolve disputes sooner over the patents the innovator held *before the biosimilar application was filed* – which are the patents the FTC believes, in the absence of any data exclusivity for innovator biologicals, innovators will base their investment decisions upon and encourage biotech companies to make the investments necessary to bring the innovator biological product to market.

- The FTC asserts that the availability of a pre-approval opportunity to assert patents will encourage biosimilar companies to challenge more patents held by the innovator.[39] In reality, the biosimilar manufacturer

[36] FTC Report at 54.
[37] FTC Report at 54-55.
[38] FTC Report at 55.
[39] *Id*.

> will have to deal with all of the patents that it infringes if it elects to infringe those patents. Otherwise, the incentives that the patent system is supposed to provide innovators, and, again, which the FTC has placed such a heavy reliance upon, will not be realized by biotechnology innovators.

Other comments in this section of the FTC Report reinforce the Commission's confusion about patent litigation realities. One significant concern raised is over the provision of the biosimilar application or information about the manufacturing of a biosimilar product to the BLA holder or other patent owners in order to enable the identification of relevant patents.[40] The FTC fails to appreciate that these interactions between patent owners and potential infringers occur in every industry, and are integral to the process of deciding whether to commence an action for patent infringement. The FTC's misplaced concerns over confidentiality and inappropriate use of information provided by a biosimilar manufacturer also are simply and routinely addressed today using standard confidentiality provisions that restrict access to and use of the information to prevent the very type of harm that the FTC envisions. Indeed, current law expressly calls for the pre-suit review of an ANDA by the NDA holder incidental to the ANDA patent notification and litigation procedures of the Hatch-Waxman Act.[41]

The FTC also criticizes the capacity of this type of process to identify and resolve all relevant patents before the biosimilar product enters the market. Of course, perfection is rarely achieved in patent litigation. The question is not whether a system can be devised that will resolve with 100% certainty every possible patent dispute. Instead, it is to create a way for motivated patent owners and biosimilar applicants to identify the patents each believes is most critical, and then to begin the process of resolving disputes over those patents as early as

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[40] FTC Report at 58.

[41] *See, e.g.*, FDCA § 505(j)(5)(C)(i)(III).

possible. The FTC's position, peculiarly, would maintain patent uncertainty for a much longer period, which somehow the FTC concludes would be beneficial to competition and consumers.

Finally, many of the FTC's competition-related concerns over a pre-approval patent litigation procedure are actually addressed in H.R. 1548. As explained above, this bill adapts the Hatch-Waxman procedures to fit the unique aspects of the biosimilar approval process (*e.g.*, the lack of a requirement for identity between the innovator and biosimilar products, the larger array of entities holding relevant patents). This bill also addresses the FTC's historical apprehension over certain features of the Hatch-Waxman system – concerns that have been largely resolved through legislative and regulatory reforms over the past decade. For example, H.R. 1548 would not impose an administrative stay of approval of the biosimilar application to permit resolution of the patent litigation. Instead, it incentivizes patent owners to expeditiously resolve litigation over key patents, providing regulatory linkage only if the patent owner prevails in the district court before the data exclusivity period for the innovator's product expires. It also preserves the ability of the biosimilar applicant to seek declaratory judgment actions to resolve concerns over patents that have not been asserted. And, critically, it permits direct participation by any patent owner, rather than attempting to funnel all potential patent disputes through the BLA holder.

4. The FTC Incorrectly Asserts that Data Exclusivity under Hatch-Waxman Is Provided Only for Unpatentable Drugs

The FTC asserts that data exclusivity provisions were implemented in the Hatch-Waxman Act to stimulate the development of new drugs when the drug molecule is not patentable, and that a longer data exclusivity period for biologics

would depart sharply from this basic trade-off because the biologic has already been incentivized through patent protection and market-based pricing.[42]

Initially, there is nothing in the legislative history of the Hatch-Waxman Act, or the statutory language of the FDCA, to support the FTC's creative re-interpretation of the Hatch-Waxman data exclusivity provisions. None of the data exclusivity provisions of the FDCA are made contingent on the absence of patent protection for a drug. In fact, the very design of the system of approval – which expressly incorporates patent resolution procedures – shows that Congress was fully aware that most drugs given data exclusivity protections will also be subject to patent rights. For example, the Act provides for early filing of an ANDA that references an NDA drug that is subject to listed patents and in which the ANDA applicant makes assertions that the listed patents are invalid or not infringed.[43] If only "unpatentable" drugs were supposed to enjoy data exclusivity protection, why would the FDCA provide for early filing of ANDA's that contain adverse patent certifications?

The FTC's confusion about the role and purpose of existing data exclusivity provisions in the FDCA reveals how fundamentally flawed its conclusions are about data exclusivity for biological products. Exclusivity provisions are available for small molecule drugs in addition to patent protection and market-based pricing, regardless of whether the drug molecule is patentable or not.[44] They do not restrict

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[42] FTC Report at 44 ("Congress has implemented exclusivity periods to encourage the development of new and innovative drug product when the drug molecule is in the public domain, and therefore not patentable.")

[43] *See, e.g.*, FDCA § 505(c)(3)(E)(ii).

[44] Notably, the FTC report only cites BIO and Harvard Professor Roin as the sources for its contrary assertion that data exclusivity is only necessary for unpatentable drugs. Both BIO and Professor Roin, however, were making the argument that the 5 years of data exclusivity provided by the Hatch-Waxman Act was *insufficient* to ensure the development of drugs with limited or questionable patent protection, and that over-reliance on the patent system

competition except in cases where the competitor seeks to free-ride on the innovator's investment in clinical research. And, substantial, peer-reviewed economic analysis shows that a substantial period of data exclusivity will be necessary to preserve the strong incentives that exist in today's system to invest in clinical trials and continue clinical development of biological products. Simply put, a substantial data exclusivity period for biologics will ensure that the best biologics will continue to be developed – not just the biologics with the best patents.

IV. Conclusions

BIO deeply appreciates the opportunity to present its views on intellectual property issues implicated by creation of a follow-on biological pathway. BIO believes that a strong case has been made that a substantial period of data exclusivity will be necessary to preserve the incentives that exist in today's biotechnology industry to bring new biological products to market, and to continue clinical development of those products after they reach the market. BIO also supports inclusion of procedures within any new abbreviated approval procedure for biologics to permit identification and enforcement of patents, and to ensure that where valid patents are found infringed by a district court, regulatory linkage will ensure that the biosimilar product is not approved and placed on the market until that valid and infringed patent expires.

(particularly under a biosimilars regime) could create suboptimal public policy outcomes under which valuable drugs might not ever get developed due to unclear patent protection. *See* Roin, *supra* at n. 8, at p. 44 ("This gap in the patent system for drugs has created a pervasive problem in the pharmaceutical industry, causing firms to regularly screen their drugs during the research-and-development process and discard ones with weak patent protection. The harm to the public from the loss of these drugs is potentially quite significant. Congress can easily avoid this problem by ensuring that the successful completion of the FDA's rigorous clinical-trial process is rewarded with a lengthy exclusivity period enforced by the FDA.).

BIO believes H.R. 1548 provides the soundest approach for implementing the incentives that are necessary to preserve continued innovation and development of biological products, and strongly encourages the Committee to support this legislation.

Attachment A

BIOTECHNOLOGY INDUSTRY ORGANIZATION
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September 30, 2008

Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Avenue, NW
Washington, DC 20580
[submitted at http://secure.commentworks.com/ftc-healthcarecompetition]

Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901 (Federal Register, September 3, 2008, Volume 73, Number 171, pp. 51479-51482, "Notice of Public Workshops and Roundtables and Opportunity for Comment")

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Federal Trade Commission (FTC) for the opportunity to respond to FTC's questions regarding competition provided by developing a regulatory approval pathway for follow-on biologic (FOB) drugs. BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, renewable sources of energy, and a cleaner and safer environment.

A. Regulatory Exclusivities and Follow-on Biologic Drug Competition

A1. What is the likely competitive effect of the market entry of a follow-on biologic competitor? Are there empirical models that predict the nature of this competition based on existing biologic drug product competition? How has competition developed between referenced and follow-on products in European markets? Would referenced product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?

The Congressional Budget Office (CBO) has estimated the savings to the federal government of S. 1695, the Biologics Price and Competition and Innovation Act of 2007, to be $5.9 billion over

the 10-year scoring window. The findings of the study confirm many of the points made below in further response to this question. The CBO score can be found at: http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf.

While BIO has not, itself, analyzed what the competitive nature of a follow-on biologics market may look like, we believe that a framework developed by Henry Grabowski and the Analysis Group can help to inform this question.[1]

This paper explains that the competitive effect of the market entry of follow-on biologic competitors will reflect the impact of an expedited approval process on both prices and utilization of each affected reference biologic product. While there is considerable heterogeneity among these innovator biologics, the paper identifies a number of critical factors that will drive these market outcomes:

- The timing of patent expiry for these products and the nature of their intellectual property protection
- The time required to develop a United States (U.S.) Food and Drug Administration (FDA) regulatory scheme, testing requirements, and any product-class guidelines following passage of any legislation
- The time required for FOB manufacturers to obtain regulatory approval (three to five years for pre-clinical and clinical testing, and one-and-a-half to two years for FDA review and approval) and to bring manufacturing capacity on-line (four to six years, likely developed concurrently with product development schedule)
- The evolution of utilization of currently approved biologics, driven by:
    - Demographics, disease incidence, medical practice, and regulatory and reimbursement practice
    - The pace and extent of uptake of next generation patent-protected products in markets where follow-on biologics have entered (limiting longer-term uptake of follow-on biologics in markets with unmet medical need)
- The nature of the competitive model in markets for biologics that experience entry by follow-on biologics (likely to be driven by the marketing of branded, proprietary products rather than the "commodity" competition based on price alone seen among generic small molecule generic drugs), and its effect on:
    - The pace and extent of uptake of follow-on products for currently marketed branded products (likely slower and less extensive than for many small-molecule drugs, or 10% to 45% follow-on product share)
    - The price impact of entry by follow-on products (limited discounts of 10% to 30% off brand, due to fewer likely market entrants than in generic drug market[2], among other factors)

[1] Grabowski, Henry, *et al*. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf

[2] Due to the higher expected development costs for a FOB product versus a generic drug, fewer market entrants are expected in the FOB market than in the generic drug market. The higher development costs associated with the development of a FOB product include, but are not limited to, manufacturing costs, costs associated with clinical trials and potentially post-marketing surveillance. For a more detailed description, please see Grabowski, Henry, *et*

The paper concludes that, with respect to cost savings in the federal budget, the magnitude of such savings is highly uncertain and very sensitive not only to the specific legislative language that emerges, but also to a range of critical assumptions about scientific, regulatory, and clinical issues, the nature of competition in markets for specific biologics, as well as future intellectual property protection, and related litigation and the development of case law.

For more detailed information, the study can be found at: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

In addition, BIO has critiqued two studies (PCMA and Express Scripts) that claimed large cost savings from a follow-on biologics pathway. The studies overestimated the savings due to, among other factors:

- Misguided estimates of the timing when savings would begin to accrue
- Unreasonable assumptions on interchangeability
- Mathematical errors

BIO's critique may be found at: http://www.bio.org/healthcare/followon/20070222.pdf.

A more recent study by Sonecon, which also suggested large savings, suffers from many of the same issues as the studies by PCMA and Express Scripts. Further, it contains a methodological error that results in an overestimate of savings of at least 110%.

The discussion above focuses on the short term. In the long run, the savings estimates are more difficult to make and depend on a number of factors, including scientific advancement.

Concerning, *"How has competition developed between referenced and follow-on products in European markets,"* the European experience to date may be of only limited value in informing what the U.S. experience will be due to the fact that very little time has elapsed since the introduction of the first biosimilar in Europe and the different ways that reimbursement occurs in Europe versus the U.S.

Concerning the final part of the question, "*Would referenced product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?*," as a trade association BIO cannot and does not discuss the strategic marketing and pricing decisions that individual member companies may or may not make.

A2. What is the likely impact of a follow-on biologic product being designated "interchangeable" (i.e., receiving an approval that would permit pharmacists, without physician authorization, to fill a prescription for the referenced product with the follow-on product)? What are the prospects for the use of "authorized follow-on biologics" in these

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al. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

circumstances? Do the answers to these questions differ based on the type of biologic product involved?

The degree of competition and potential cost savings arising from a follow-on biologics approval pathway is likely to be dependent on numerous factors, including product quality, cost of production, price discounting, market penetration, number of market entrants, potential market size for any given product, etc. For more detail, please see our answer in response to Question # 1 above.

With respect to designations of interchangeability, it is BIO's position that patients and their physicians should decide the proper course of treatment, including which medicine to take. All biologics should be dispensed as written and prescribed by brand name. We are urging Congress to ensure this approach in any legislation. Indeed, FDA recently stated:

> With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.[3]

The complex nature of biological manufacturing methods means that the manufacturing process used by a follow-on manufacturer will be different from the manufacturing process of the innovator. Because a follow-on manufacturer can never exactly duplicate the innovator's process, differences in process may result in differences in the protein product and, significantly, different effects in the clinic. In fact, even when innovator companies make changes in their *own* manufacturing processes, unanticipated changes in the product can and have occurred. For specific examples of such situations, please see our comments to the European Medicines Agency (EMEA) and FDA, available at http://www.bio.org/healthcare/followon/ (e.g., BIO Comments to 2004N-0355, "Scientific Considerations," December 13, 2004, pp. 18-37). Based on the experience of innovators, BIO agrees with FDA that it has not been determined how interchangeability can be established for complex proteins made by separate manufacturers.

If pharmacists were able, without physician authorization, to substitute the follow-on product for the reference product, patients might not only be dispensed a follow-on biologic rather than the prescribed biologic, but they might be switched back-and-forth among several products over time. Although switching among the innovator small-molecule drug and its generic versions normally raises few concerns, switching among biologics that are "similar" – rather than the same – involves particular risks. As FDA notes:

> For many follow-on protein products – and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.[4]

[3] http://www.fda.gov/cder/news/biosimilars.htm, Possible International Non-proprietary Name (INN) Policies for Biosimilars, September 1, 2006

[4] http://www.fda.gov/ola/2007/protein32607.html, Statement of Janet Woodcock, M.D., before House Committee on Oversight and Government Reform, March 26, 2007

EMEA and certain member states of the European Union likewise have recognized the fundamental differences between drugs and biologics with respect to substitutability. Recently, EMEA issued a statement that "[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional." BIO believes that, consistent with the policies of EMEA and many European countries, patients should receive the product expressly prescribed by a physician.

It is important to note that substitution has been a problem for certain small molecule generics. For example, levothyroxine, the generic form of certain medications treating hypothyroidism, is only safe and effective at a very narrowly defined dose. The American Thyroid Association has issued a public statement noting that patients should be alerted by their physicians or pharmacists that their levothyroxine preparation might be switched at the pharmacy, that patients should ask to remain on their current levothyroxine preparation, and that they should inform their physicians if their thyroid hormone is changed to a generic preparation because, following such a switch, thyroid function should be re-checked. This concern is even more relevant for biologics, which are often hundreds or thousands of times larger and more complex than traditional chemical drugs. The kinds and sizes of studies that would have to be done to address doubts about substitutability – including the risks of switching – would be so large that the dataset presented for approval would likely be larger than that required to be presented by an innovator.

As Secretary Leavitt noted in a letter to Senator Kennedy:

> [I]n light of the current scientific limitations on the ability to make determinations for interchangeability, and because it is critical to protect patient safety, the Administration believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician, and legislation should not allow for determinations of interchangeability at this time.[5]

Finally, we caution that the term "interchangeability" is not defined by FDA and has no settled legal or regulatory meaning at this time. We note that some use this word to describe products that are not "substitutable" or "therapeutically equivalent," but which, under a physician's supervision, could be used to treat the same disease or condition in the same patient.

Concerning the question, *"What are the prospects for the use of `authorized follow-on biologics' in these circumstances?,"* as a trade association, BIO cannot and does not discuss the strategic marketing and pricing decisions that individual member companies may or may not make.

A4. How would the prospect of competition from follow-on biologic drugs influence research and development for new biologic drugs, improvements to existing biologic drugs, and the timing and rollout of new and/or improved biologic drugs? Does the market experience with non-biologic generic pharmaceutical drug products provide insights into these issues?

[5] Letter from HHS Secretary Michael O. Leavitt to Senator Edward M Kennedy, June 26, 2007

When discussing future innovation, it is helpful to understand what biotechnological innovation has accomplished to date. Biotechnology has created hundreds of new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders, and many other rare and unmet medical conditions. In fact, between 1995 and 2005, 160 different medicines were approved to treat rare diseases that affect 200,000 or fewer patients. Biotechnology also is responsible for hundreds of medical diagnostic tests that keep the blood supply safe and detect other conditions early enough to be successfully treated.

This spectacular innovation depends on an environment where companies can attract the capital needed to continue massive research and development (R&D) investment. Over the past 25 years, the average R&D intensity (R&D spending to total firm assets) for biotechnology was 38%. By comparison, the average R&D intensity for all industries was only about 3%.[6] According to Ernst and Young, "Global Year in Review 2006," the biotechnology industry has increased the amount of money it devotes to R&D by more than 120% since 1994.[7] Biotechnology is one of the most research-intensive industries in the world. The U.S. biotech industry spent $19.8 billion on research and development in 2005 alone.

In this regard, it bears emphasis that the biotechnology industry in the U.S. is still relatively nascent and largely unprofitable: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies – many of which will never see a product come to market or turn a profit – that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology companies (all biotechnology companies but the top 10) account for two-thirds of the industry's future clinical pipeline.*[8]

This enormous reservoir of biotech innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients. Thus, in crafting a follow-on biologics approval pathway, it is important to err on the side of incentivizing innovation, particularly in light of the unique elements of the biotechnology industry. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research – which is particularly difficult in the current economic environment. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted follow-on biologics regime.

The statistics speak to the challenges this emerging industry faces. Biologics research and development is a high-risk endeavor, with higher capital costs, higher material costs, greater

[6] Golec, Joseph H. and John A. Vernon. "Financial Risk in the Biotechnology Industry," NBER Working Paper 13604.

[7] Ernst & Young LLP, annual biotechnology industry reports, 1993–2006. Financial data based primarily on fiscal-year financial statements of publicly-traded companies; constant 2005 dollars.

[8] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

manufacturing costs and uncertainties, longer development times, and lower late-stage success rates than compared to small molecule drugs. In fact, from 2001–2005, the success rate of a Phase III trial for the average biotechnology product was just slightly more than 50%.[9] These failures occur at the last stage of product development – after years of research and hundreds of millions of dollars may have been spent.

The industry's heavy reliance on private equity also is notable. In 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:[10,11]

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Net Loss ($B)	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	1.4	3.5

This situation is very much *unlike* the situation involving the traditional small molecule pharmaceutical market at the time that the Hatch-Waxman Act created a generic drug pathway in 1984 – a market that was dominated by mature and profitable companies with substantial revenues to reinvest in pharmaceutical R&D. Thus, the risk of driving research investment out of the industry, and quite possibly out of the U.S., is substantial if a follow-on biologics approval pathway does not contain sufficient incentives for continued innovation.

Given these unique challenges, patent protection alone (even including patent term restoration under current law) is not sufficient to ensure such adequate incentives under a follow-on biologics regime. Under a statutory framework allowing for follow-on biologics, there is a very real potential that the manufacturer of a follow-on product may be able to secure regulatory approval based at least in part on the innovator's prior approval, and, at the same time, avoid infringing patents that protect the innovator's product. That likelihood exists because of the confluence of critical factors not present in the Hatch-Waxman Act construct for generic small molecule drugs. Unlike a generic drug which must be the same as an innovator product, a follow-on biologic will only be required to be "comparable," "similar' or "highly similar" to the corresponding innovator product. Compared to generic drugs, the emerging follow-on biologics framework thus provides applicants with significantly more leeway to design around the patents that claim the reference product and make products that are sufficiently different to avoid patent infringement, but sufficiently similar to get abbreviated regulatory approval.

[9] Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.

[10] Ernst and Young LLP, annual biotechnology industry reports, 1995 – 2007. Financial data based primarily on fiscal-year financial statements of publicly-traded companies.

[11] Only about 20 biotech companies are currently profitable: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

In light of this increased risk due to the scientific and regulatory facts related to biologics, data exclusivity must be substantially longer than the five years currently afforded to small molecule drugs under the Hatch-Waxman Act. Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies, in order to secure the necessary resources from venture capital firms and other funding sources, must have some certainty that they can prevent free-riding on their investment in the development of new breakthrough therapies for a substantial period of time. Without sufficient data protection, companies and investors will have a great deal of uncertainty as to whether they will be able to recoup the – on average – $1.2 billion in research and development costs that are necessary to bring a biologic to market.[12] This large amount of uncertainty will cause companies and investors to direct their investments to other areas where there is a higher degree of certainty that they will obtain a fair return on their investment.

This decrease in biotechnology R&D investment will be detrimental not just to biotechnology companies, but also to American universities, as less of their cutting-edge research and fewer of their technologies will be licensed because companies will not be able to recoup the R&D investment necessary to take a licensed technology from the laboratory to the marketplace. Investors will turn to other less risky ventures, and cutting-edge research (including the substantial public investment in basic research through the National Institutes of Health) will sit on laboratory shelves, as it often did prior to the Bayh-Dole Act and the Hatch-Waxman Act patent term restoration provisions.

If this occurs, society as a whole will suffer. New treatments in the pipeline hold the promise of continued progress against our most pressing medical challenges. At present, more than 400 biotechnology medicines and vaccines are in development, targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis. Specifically, there are:

- 210 for cancer and related conditions
- 22 for cardiovascular disease
- 15 for diabetes and related conditions

These innovative treatments include:

- Monoclonal antibodies to treat asthma, Crohn's disease, and lupus
- Therapeutic vaccines for AIDS
- Recombinant proteins to treat autoimmune disorders

Without adequate incentives these – and many other – breakthrough cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions may either take longer to come to fruition or not come to be realized at all.

[12] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

A properly developed follow-on biologic pathway will ensure that the incentives needed to encourage research and development of new, innovative therapies remain in place. BIO believes that, to accomplish this result, the best data available support a 14-year period of data exclusivity for biologics under a follow-on biologics regime. We emphasize that data exclusivity does not interfere with the existing competition among biologic innovators today, and we are not seeking "marketing exclusivity" to prevent such competition. Rather, data exclusivity only prevents, during this time period, a follow-on manufacturer from short-circuiting the normal FDA approval process by basing its FDA application on the safety and efficacy of the innovator product rather than its own full application.

Several independent factors support BIO's position on the appropriate data exclusivity period. First, we know that the breakeven point for return on investment in a biologic occurs after it has been on the market between 12.9 and 16.2 years,[13] and thus competition from follow-on biologics prior to that time period would clearly undermine incentives for such investment in the first place. Second, in 1984, Congress enacted patent term restoration provisions to provide pharmaceuticals with up to 14 years of patent protection following marketing approval. This time period was selected so that "research intensive companies will have the necessary incentive to increase their research and development activities."[14] As a result, the average period of time for marketing a drug product with patent protection now is 11.5 years,[15] and new molecular entities are, on average, marketed in the U.S. for 13.5 years before the entry of generic competition.[16] A similar length of protection should be available for biologics. For a fuller discussion of these data and the justification for 14 years of data exclusivity, please visit the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

In addition, a follow-on biologics pathway must maintain incentives for the development of second-generation products.[17] A second-generation product must go through the same rigorous FDA approval process as a first generation product. It requires development and submission of full clinical safety and efficacy data to support FDA review and approval of the complete marketing application (Biologics License Application (BLA) or New Drug Application (NDA)). Accordingly, FDA approval of a second-generation product should be rewarded with full data

[13] Grabowski, Henry. "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper. June 2007.

[14] H.R. Rep. No. 98-857, at 41 (1984).

[15] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

[16] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics 28(4-5), pages: 491-502 (2007).

[17] "…second-generation products – those with structural differences designed to improve performance while maintaining the same mechanism of action as the original product – are not conventionally considered as follow-on products." Woodcock, J., "The FDA's Assessment of Follow-on Protein Products: A Historical Perspective," Nature Reviews Drug Discovery 6: 437-442, June 2007.

exclusivity as well. Such exclusivity is necessary to enable manufacturers to invest in the development of such innovative second-generation products and to enable patients to benefit from these treatment advances. Simply put, without sufficient data exclusivity of their own, second generation products will not be developed if a follow-on biologics pathway is enacted. Such a result would be a "lose-lose-lose" situation. A loss for innovators who would not pursue product improvements, a loss for follow-on manufacturers who would not have second-generation products to select from, and most important, a loss for patients who would not have the benefit of improved products.

For new indications, there should be an additional data exclusivity period for the original innovative product (e.g., 2 additional years) as an incentive for innovators to invest in such advances. Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time. Without this additional exclusivity, there would be little incentive to research and obtain approval for these new indications.

BIO notes that data protection for a second-generation product will in no way affect the ability of a follow-on biologic to enter the market based on the original innovative product. The success of the second-generation product will depend on its benefits for patients and price compared to the follow-on and other competitive marketed products. If the second-generation product's benefit is minor in comparison to existing products, then it is unlikely – particularly in today's price-sensitive payer market – that granting data exclusivity to the second-generation product will impact the marketplace in any meaningful way. However, without any separate data exclusivity for second-generation products, major advances will be stymied.

A6. How are the patent portfolios claiming biologic drugs similar or dissimilar to the patent portfolios that claim small molecule (nonbiologic) drugs approved under the federal Food, Drug, and Cosmetic Act (FDCA)?

There is less public information available about patent portfolios for biologics than for small molecule drugs. However, certain inferences about such patent portfolios can be drawn from current biotechnology patent practice, and from biotechnology patents known to cover existing FDA approved biologics.

Like small molecule drugs, biologics are protected by different classes of patent claims, but there are critical distinctions:

(a) Compound claims. Claims to the active molecule, such as a specific peptide or antibody, exist for biologics, as they do for small molecule drugs. The way in which these active molecules are claimed, however, is often significantly different. For example, unlike small molecules, biologics are often claimed with reference to specific amino acid and/or nucleic acid sequences, and more often include functional claim limitations.[18]

[18] For example, an antibody claim that includes a sequence limitation in addition to multiple functional limitations could be drafted in the following form:

(b) Claims to methods of treatment (use of the compound in a specific indication; dose, route, or schedule of administration, etc.) exist, as they do for small molecule drugs.[19]

(c) Drug product claims (formulation, dosage form) exist, as they do for small molecule drugs.[20]

(d) Product by process claims are more prevalent and important in biotechnology than in small molecule medicinal chemistry. In a biotechnology product-by-process claim, the claimed molecule is defined not (or not solely) by its molecular structure or by its function, but as the product resulting from following the steps of a biotechnological process. Such claims are useful in cases where important characteristics of the claimed molecule depend on the process by which it was made (see below), but where it may not be possible or feasible to otherwise describe all such characteristics in structural and functional terms. This is sometimes the case for inventions that comprise complex mixtures of different compounds (e.g., a vaccine).[21]

(e) Claims that protect manufacturing technology: Process claims. Claims to manufacturing processes are more important in biotechnology than they are in the small molecule space.[22] The

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"An isolated human antibody, or an antigen-binding portion thereof, that dissociates from human [antigen] with a K_d of $1x10^{-8}$ M or less and a K_{off} rate constant of $1x10^{-3}$ or less, both determined by surface plasmon resonance, and neutralizes human [antigen] cytotoxicity in a standard in vitro L929 assay with an IC_{50} of $1x10^{-7}$ M or less, said antibody comprising a heavy chain variable region comprising a contiguous sequence from CDR1 through CDR3 as represented in SEQ ID NO:14."

In such a claim, the reader would consult the attached patent specification to identify the specific sequence of amino acids that make up the critical portion of the claimed antibody.

[19] An example of a biotechnology claim to a method of treatment could be drafted in the following form:

" A method for inhibiting the growth of human tumor cells that express human [factor] receptors and are mitogenically stimulated by [factor], the method comprising administering an effective amount of an anti-neoplastic agent and an effective amount of a monoclonal antibody to a human cancer patient having said tumor cells; (i) wherein said antibody binds to the extra-cellular domain of the human [factor] receptor of said tumor cell; (ii) wherein the antibody is not conjugated to the anti-neoplastic agent; and (iii) wherein the antibody inhibits the binding of [factor] to the [factor] receptor."

[20] An example of a biological composition claim could be as follows:

" A pharmaceutical composition for parenteral administration to a human patient comprising human [enzyme] with catalytic activity and in a therapeutically effective dosage to treat a patient suffering from [syndrome]; and a pharmaceutical carrier, the composition being free of other human proteins present in its natural environment."

[21] An example of a biological product-by-process claim could be:

"A bacterin-toxoid vaccine against [bacterial strain] infection produced by culturing [bacterial strain] for a time sufficient for said culture to reach the late-logarithmic phase of growth; harvesting culture supernatant therefrom comprising leukotoxin, capsular antigen, soluble antigens, and [bacterial] cells at a density ranging from about 10^3 to about 10^8 cells per ml; and adding an inactivating agent."

[22] An example of a biotechnological process claim could be drafted as follows:

processes by which biologics are made are highly specific, complex, and determine many of the biologic's functional and structural characteristics, such as the way the protein is folded; the presence and position of sugar or fatty acid side chains; the way proteins aggregate; the way both ends of the protein's amino acid chain are truncated or extended; the presence of protein isoforms in the final preparation, or its impurity profile, and the like. Such product characteristics can often be expected to affect the product's safety, purity, and efficacy profile, and thus are integral to the approval of the product itself. Thus, many important inventions are made as biologics manufacturers work out optimal processes to reliably and reproducibly make, purify, and process a biologic molecule. In contrast to the Hatch-Waxman Act, which does not permit listing of process patents and excludes them from the Act's patent resolution procedures, FOBs legislation should contain adequate provisions to account for the importance of process patents in the biologics space, and allow for the pre-marketing resolution of disputes over such patents.

(f) Claims that protect manufacturing technology: Non-process claims. The high importance of process technology is also illustrated by the existence of patents on inventions that must be practiced as part of the technology platform necessary to make and use the biologic, such as claims to the isolated and purified DNA or RNA polynucleotide that encodes the recombinant protein, to the vector used to insert it into host cells, to the host cell that secretes it, to the promoter that drives its expression, and the like. The existence and importance of such claims relate to the way biotechnology inventions are made as the technology progresses through clinical and process development to market approval. The discovery of a new receptor on certain cancer cells, for example, may lead to the isolation and purification of the receptor protein and the sequencing of its amino acid sequence and of the gene that encodes it. To transform such basic discoveries into real-world therapeutic products, biologics manufacturers must develop a technology platform that can involve a number of independently patentable inventions, such as hybridoma cells that secrete antibodies to the drug target, the construction of vectors useful to transfer it to cultured cells, techniques to regulate its expression, and the like. This way, developing, making and using a biotechnology product can involve multiple patentable inventions that all must be practiced together. Patents on such inventions play a more prominent role in the portfolios that protect biologic drugs compared to the small molecule sector.[23] Despite

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"A process of making a conjugate that comprises a [protein] glycoprotein having an N-terminal alpha-amino group and one poly(ethylene glycol); said process comprising: a) expressing and fermenting a recombinant [protein] that has an N-terminal peptidic extension that includes a proteolytic cleavage sequence, b) protecting the .epsilon.-amino groups, c) proteolytically cleaving the N-terminal peptidic extension, d) pegylating the N-terminal .alpha.-amino group, and e) deprotecting the .epsilon.-amino groups of the [protein] glycoprotein; wherein the recombinant [protein] comprises a sequence selected from the group consisting of the amino acid sequences SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO 4: and SEQ ID NO: 5."

[23] Examples of DNA or host cell claims that are part of the technology platform for manufacturing a therapeutic protein could be drafted as follows:

"An isolated DNA molecule encoding a protein comprising a sequence of amino acids selected from the group consisting of amino acids 1-142 of SEQ ID NO:1 and amino acids 1-226 of SEQ ID NO:3, wherein said protein is capable of binding [receptor]."

"A eukaryotic host cell containing DNA encoding an antibody molecule, said antibody being capable of being expressed in said eukaryotic host by said DNA, wherein said antibody has specificity for the antigen bound by the

their importance to the protection of biologics process technology today, it is possible that the relevance of such patents would be diminished under a FOBs regime where many FOB products would be produced overseas, as more fully explained in BIO's answer to Question #3 in the patent section, below.

Deposits of biological material are another aspect without correlate in the small molecule space. Every patent must contain a technical disclosure sufficient to enable other skilled persons to make and use the invention without undue experimentation. In biotechnology, however, inventions may not always be easily reproducible. For example, during a transfection experiment (a form of experimental gene transfer) it is not possible to predict exactly where, and how, a piece of foreign DNA will be integrated into the chromosomes of the host cell. Each successfully transfected cell will be unique in its own way, and may be near impossible to exactly reproduce by repeating the experiment. Other biotechnology inventions involve complex biological materials that cannot sufficiently be described by words alone. In such situations, the patent law requirement that a patent "enable" other skilled persons to make and use the invention can be satisfied by providing a sample of the biological material to a depository that is approved by the World Intellectual Property Organization, such as, for example, the American Type Culture Collection, where it can be accessed and studied by others. Some biologic drug claims that reference deposited biologic materials are narrowly limited in their scope to only what was deposited.[24]

Other aspects of patent law, too, impact the way biologic drugs are claimed and the amount of experimental work that must be done to obtain comprehensive patent protection. Patent applicants who seek broader biotechnology claims must often conduct more experiments, do more work, and provide more in-depth explanation of the underlying biological processes and structure-function relationships than their colleagues in the small molecule field. This work must be done to satisfy the so-called "written description" and "enablement" requirements – a task that can be particularly difficult in biotechnology, where the unpredictability of biological processes may not allow other scientists to extrapolate from just a few described examples to the full scope of a broadly-claimed invention, and to practice it across its full scope without undue experimentation. Many biotechnology patent practitioners feel that the "written description" and "enablement" requirements operate to limit the breadth of claims available to patent applicants.[25] Stringent application of these requirements by patent examiners may also force patent applicants to retreat from an initially broader claim scope to a much narrower claim scope during the course of patent examination. Because such surrendered claim scope can be difficult or impossible to

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antibody produced by hybridoma [###] as deposited with the ATCC, and wherein said antibody has cytolytic activity."

[24] An example of a biotechnology claim that includes a limitation to a specific deposit could be drafted as follows:

"A method for treatment of [specific cancer] comprising the step of administering a therapeutically effective amount of immunologically active anti-[antigen] antibody to a patient in need thereof, said antibody being derived from a hybridoma as deposited with the ATCC, deposit number [###]."

[25] For a recent interpretation of the so-called "written description" requirement, see *Carnegie Mellon University et al. v. Hoffmann-La Roche Inc. et al*., Slip op. (Fed Cir. Sept. 8, 2008); available at: http://www.cafc.uscourts.gov/opinions/07-1266.pdf.

regain during enforcement in later litigation, patentees may find themselves confined to the literal limits of their issued claims, and unable to assert that even a close equivalent of their own, patented product infringes the patent.[26]

In summary, while sharing some common features with small molecule patents, biologics patents more commonly include functional claim limitations, may be limited in scope to specific deposited biological materials or specific recited sequences, and often face unique challenges in meeting the written description and enablement requirements. When viewed as a whole, the patent portfolios that protect biologic drugs today are often more complex than those found in the small molecule space. These differences cannot be disregarded when crafting any follow-on biologics approval pathway. However, for the reasons set forth in BIO's answer to Question #3 in the patent section, below, it does not follow that higher complexity in the innovators' patent estates would always translate into more complex patent litigation. Instead, differences in the way patent disputes would be resolved would predominantly be grounded not in portfolio complexity, but in the way these portfolios operate under different approval standards for generic drugs and FOBs. In the small molecule space, a patent that claims an innovator's new molecular entity almost certainly also covers the generic drug applicant's molecule, because both must, by law, be "the same." Under a follow-on biologics regime, FOB products would likely be approvable under a less stringent standard that may provide FOB applicants with significantly wider latitude to design around innovator patents, and to manufacture FOB products that are different enough to avoid patent infringement, yet similar enough to benefit from the reference product's safety and efficacy record and obtain abbreviated approval. Thus, the differences between patent portfolios that claim small molecule drugs and biologics must always be examined in the regulatory context in which these portfolios will be brought to bear. This context must be taken into account when designing patent resolution procedures in any FOBs regime.

A7. Are the regulatory exclusivities currently provided to pharmaceutical drug products in the FDCA appropriate for new biologic drugs and/or significant improvements to existing biologic products? Are they appropriate for specific types of biologics? Why or why not?

BIO believes that the balance between innovation and generic competition struck by the Hatch-Waxman Act can provide valuable insights for the development of a follow-on biologics approval pathway. The Hatch-Waxman Act provides innovators and generic competitors a range of statutory, patent, and litigation-based incentives that, as described in response to a previous question, operate to create de facto protection against generic competition for, on average, 13.5 years. However, to achieve that same balance in the follow-on biologics context, the law must reflect the differences between small molecule drugs and biologics and differences between generic drugs and follow-on biologics. Under the 1984 Hatch-Waxman Act, a generic version of a small molecule drug may be approved for marketing only if its active ingredient is the "same" as in the innovator product. Thus, the patents that cover the innovator's active ingredient generally will apply to the generic version. Accordingly, the generic drug manufacturer cannot

[26] For a recent discussion of developments in the patent law doctrines relating to prosecution history estoppel and equivalence, see, e.g., John R. Allison and Mark A. Lemley, The (Unnoticed) Demise of the Doctrine of Equivalents, 59 Stan. L. Rev. 955 (2007).

gain FDA approval of its product by demonstrating that the active ingredient is the same as the innovator product and then claim in the patent context that it is different from the innovator's drug. In addition, the Hatch-Waxman Act contains provisions that can extend the term of an innovator patent to cover a period of 14 years following approval of an innovative drug. As noted above, new molecular entities today do not face generic market competition until 13.5 years post-FDA approval on average, evidencing that the mix of policy tools employed by the Hatch-Waxman Act has come remarkably close to achieving the 14-year mark deemed appropriate under the Act for innovators to recoup their substantial investments prior to generic entry.

In contrast, under the various statutory frameworks being considered for follow-on biologics, a follow-on will not be required to be the "same" as the innovator product due to the high degree of complexity of biologics. Instead, the follow-on product will only have to be similar or highly similar to the innovator product. This similarity standard for follow-on biologics creates a significant risk that a follow-on competitor will circumvent or "design around" the innovator's biotech patents – meaning that the follow-on may be outside of the scope of the innovator's patent claim. As a result, a follow-on biologic may be sufficiently similar to the innovator biologic to rely to some degree on the safety and effectiveness of the innovator product and thus receive abbreviated regulatory approval. Yet, it may still be different enough from the innovator product to avoid a patent infringement claim and, thus, reach the market well in advance of innovator patent expiration. For these reasons, patents may provide less comprehensive protection for innovative biologics under a follow-on biologics regime than they do for small molecules in the generic drug context.

Accordingly, if data exclusivity in a follow-on biologics regime were limited to the 5 years under the Hatch-Waxman Act, it would severely undermine incentives to invest in biotech innovation. Instead, BIO believes that a 14-year period of data exclusivity should be granted for biologics in any follow-on biologics regime. Such an approach would ensure that biologics receive the same degree of effective market protection from follow-on competition that small molecules receive today from generics, as described above. For more detailed information, please see BIO's response to Questions #4 above and #8 below, as well as our white paper on exclusivity and patent protection in a follow-on biologics regime, found at the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

A8. What are the appropriate factors to consider when determining the optimal length of regulatory exclusivity periods for biologic drug products? Do these factors change based on the type of referenced product involved, the extent of competition facing the referenced product, or patent portfolios claiming the referenced product, and if so, how?

The biotechnology industry in the U.S. is still relatively nascent and largely unprofitable: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies – many of which will never see a product come to market or turn a profit – that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology*

companies (all biotechnology companies but the top ten) account for two-thirds of the industry's future clinical pipeline.[27]

This enormous reservoir of biotech innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients. Thus, in crafting a follow-on biologics approval pathway, it is important to err on the side of incentivizing innovation, particularly in light of the unique elements of the biotechnology industry. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted follow-on biologics regime.

The industry's heavy reliance on private equity also is notable. In 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:[28,29]

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Net Loss ($B)	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	1.4	3.5

Given these unique challenges, patent protection (including patent term restoration under current law) is not sufficient to ensure adequate incentives for biotech innovation under a follow-on biologics regime. Rather, any statutory pathway for follow-on biologics must establish a substantial period of data exclusivity to preserve incentives for research, development, manufacture, and approval of new biologic therapies. As discussed in response to Questions #4, 6 and 7, this is necessary because, under a statutory framework allowing for follow-on biologics, there is a very real risk that the manufacturer of a follow-on product may be able to secure abbreviated regulatory approval based at least in part on the innovator's prior approval, and, at the same time, avoid infringing the patents that protect the innovator's product. That likelihood exists because of the confluence of critical factors not present in the Hatch-Waxman Act construct for generic small molecule drugs. Unlike a generic drug which must be the same as an innovator product, a follow-on biologic will only be required to be "comparable," "similar' or "highly similar" to the corresponding innovator product. Compared to generic drugs, the emerging follow-on biologics framework thus provides applicants with significantly more leeway to design around the patents that claim the reference product and make products that are

[27] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

[28] Ernst and Young LLP, Annual biotechnology industry reports, 1995 – 2006. Financial data based primarily on fiscal-year financial statements of publicly-traded companies.

[29] Only about 20 biotech companies are currently profitable: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

sufficiently different to avoid patent infringement, but sufficiently similar to get abbreviated regulatory approval.

In light of this potential gap in patent protection for biologics under a follow-on biologics regime, data exclusivity must be substantially longer than the five years currently afforded to small molecule drugs under the Hatch-Waxman Act. Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies, in order to secure the necessary resources from venture capital firms and other funding sources, must have some certainty that they can prevent free-riding on their investment in the development of new breakthrough therapies for a substantial period of time. Without sufficient data protection, companies and investors will have a great deal of uncertainty as to whether they will be able to recoup the – on average – $1.2 billion in research and development costs that are necessary to bring a biologic to market.[30] This large amount of uncertainty will cause companies and investors to direct their investments to other areas where there is a higher degree of certainty that they will obtain a fair return on their investment. If this occurs, society as a whole will suffer, as fewer cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions will be developed.

As stated above, BIO believes that the best data available support a 14-year period of data exclusivity – not an "exclusive marketing" period – for biologics under a follow-on biologics regime. Several independent factors support this position. First, we know that the breakeven point for return on investment in a biologic occurs after it has been on the market between 12.9 and 16.2 years,[31] and thus competition from follow-on biologics prior to that time period would clearly undermine incentives for such investment in the first place. Second, in 1984, Congress enacted patent term restoration provisions to provide pharmaceuticals with up to 14 years of patent protection following marketing approval. This time period was selected so that "research intensive companies will have the necessary incentive to increase their research and development activities."[32] As a result, the average period of time for marketing a drug product with patent protection now is 11.5 years,[33] and new molecular entities are, on average, marketed in the U.S. for 13.5 years before the entry of generic competition.[34]

[30] DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" Managerial and Decision Economics 28(4-5), pages: 469-479 (2007).

[31] Grabowski, Henry. "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper. June 2007.

[32] H.R. Rep. No. 98-857, at 41 (1984).

[33] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

[34] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics 28(4-5), pages: 491-502 (2007).

Thus, any statutory formula that allows for follow-on biologics should at least guarantee the same degree of effective market protection that Congress found necessary to maintain incentives for innovation in small molecule drugs – and, for the reasons discussed above, that protection can be accomplished most predictably through data exclusivity. Indeed, if the data exclusivity period for biologics is less than the number of years available to drugs under patent term restoration (that is, 14 years), then, because of the potential patent protection gap and the higher risks of biologics development, it will skew investment away from biotech innovation. Because data exclusivity would run concurrently with the patent term for the product, it therefore would create actual protection only in those instances where the follow-on manufacturer would be able to work around the patents held by the innovator but still gain abbreviated approval of its product.

For a fuller discussion of these data and the justification for 14 years of data exclusivity, please visit the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

A9. How does the European Medicines Agency's approach to regulatory exclusivities in its abbreviated regulatory approval pathway for follow-on biologics inform the U.S. approach?

As we state in our answers above, we believe that a 14-year base period of data exclusivity is necessary to avoid undermining incentives for the development of innovative biologics. And for the reasons explained more fully below, anything less would jeopardize the U.S.'s leadership role in producing innovative biotechnology medicines for the patients who need them.

The European Union provides eight years following innovator approval during which a generic or biosimilar application cannot be submitted, two further years (i.e., 10 years total) during which a generic or biosimilar cannot be marketed, and one further year if, during the first eight years of data exclusivity, the holder of the reference product obtains an authorization for new therapeutic indication(s) which bring(s) significant clinical benefit in comparison with existing therapies. While we believe that the length of data exclusivity provided in the European Union would be inadequate in the U.S. context, we strongly agree with the provision of a further exclusivity period for new indications, and we also note that the European Union provides 10 (or 11 if appropriate) years of data exclusivity to next- or second-generation products. (See BIO's Response to Question #4 above). We also strongly support the protection against the filing of biosimilar applications too soon after innovator approval, for the reasons described more fully in response to Question #1 below in the patent section).

We believe that if the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, the result will be substantially less investment in biotech innovation. Because the U.S. leads the world in this area, the economic impact of reduced investment will be particularly acute here in the U.S. The latest data from Burrill & Company show that the U.S. continues to dominate the biopharmaceutical market, whether the measure is sales, R&D, employees or public companies:

US, European, Canadian, Japanese, Canadian, and Australian Biotech: Global Activity Measures (2005, U.S. dollars)

	U.S.	Europe	Japan*	Canada	Australia
Sales/Revenue	$71.5 B	$7.5 B	$0.82 B	$1.7 B	$1.0 B
Annual R&D	$18.5 B	$4.2 B	-	$0.6 B	$0.1 B
# of Companies	1,473	1,878	464	470	226
# of public companies	363	96	22	81	58
# of employees	146,100	32,470	4,171	7,440	6,393

*Japan – public companies only

The U.S.'s per capita biotech R&D expenditures are 574% higher than the European Union's (EU's) per capita biotech R&D expenditures.[35] It also should be noted that:[36]

- The biotechnology industry's U.S. trade surplus grew from $593 million in 2000 to $1.8 billion in 2004 – an increase of almost 200%. Over the same period of time, overall U.S. trade in advanced-technology products decreased by more than 200% -- going from a net surplus to a net deficit.
- The biotechnology industry's U.S. exports grew from $1.7 billion in 2000 to $3.7 billion in 2004 – an increase of more than 100%.
- Between 2000 and 2004, U.S. jobs in the biopharmaceutical industry rose by 8.3%.
- The biopharmaceutical industry expands U.S. gross domestic product by at least $27 billion annually, on a permanent basis, for every one-time R&D investment of $15 billion. In 2005 alone, the U.S. biotechnology industry invested nearly $20 billion in R&D.

Thus, a follow-on biologics pathway that does not preserve the necessary incentives for innovation (that is, 14 years of data exclusivity) would disproportionately and negatively affect the U.S., the world leader in biotechnology innovation, and would drive investment towards less risky ventures, including those outside of the U.S.

B. Patent Dispute Resolution Issues

B1. Would it be important to have the litigation of any patent disputes proceed concurrently with the abbreviated FDA approval process for follow-on biologics? Why or why not? What has been learned from the experience under Hatch-Waxman about the incentives necessary to encourage early resolution of patent issues?

It would be important to resolve patent disputes concurrently with the approval process, and prior to launch of, a follow-on biologic, because premature launches of such products carry numerous risks that significantly impact the public as well as the private interests of the parties.

[35] R&D figures are from Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007. Population figures estimated as of July 2006.

[36] See URL: http://www.nsf.gov/statistics/seind06/c6/tt06-03.htm -- last accessed on February 1, 2008.

A judicial determination of patent infringement for a prematurely-launched FOB product would raise significant concerns about therapeutic disruption for patients. In fact, consistency of product availability is of great importance to patient health and physician prescribing practices and such consistency would be jeopardized by a premature launch without patent resolution.

Premature marketing would not only create unnecessary confusion among physicians, patients, payers and other market participants – it would also lead to great business uncertainty for both parties. From the reference product sponsor's perspective, a premature follow-on biologic launch may lead to a loss of market share and price erosion that cannot be reversed even if a court subsequently were to find the asserted patents valid and infringed. From the follow-on applicant's perspective, a judicial determination of patent infringement could lead to very significant damages awards which may or may not exceed the applicant's financial capacities.

Seen this way, launches of follow-on biologics prior to patent resolution entail huge business risk not only for the innovator, but also for the follow-on applicant – a risk that is exacerbated by the considerable financial investment in FOB development (much larger than the investment required for a generic drug submission) that would already have been made at that point. It stands to reason that only the biggest, financially strongest FOB applicants would tolerate the risk of losing their investment or facing large infringement damages awards. Thus, a FOB framework that routinely envisions patent resolution after FOB market entry would selectively disadvantage smaller, financially weaker FOB applicants and operate to create FOB markets that are dominated by only a few, financially strong players and FOB products.

Sufficient time for resolution of patent disputes prior to follow-on biologic approval must therefore be provided. Ideally, patent disputes would be resolved by the time the innovator statutory exclusivity period expires. This way, the patent resolution could take place without the need for special stays pending litigation during a time when the FOB product could otherwise be launched. Such timing of patent resolution would provide business certainty that a risk-free FOB launch could occur at a fixed point in time. Timing of patent resolution prior to the expiration of the innovator's statutory exclusivity period would also encourage full resolution of patent validity questions on the merits, rather than through settlement, thus providing more patent certainty for subsequent FOB applicants.

However, while patent resolution should be timed so as to be concluded within the innovator's statutory exclusivity period, it should not be timed so as to begin too early. The FOB applicant must be far enough down the road of developing its comprehensive data package, as well as its detailed manufacturing processes, needed for the FOB regulatory submission and for a full exploration of relevant patent-related issues. Further, in order to properly evaluate a FOB application and the heightened concerns regarding immunogenicity in the biologics arena, the FDA will need sufficient experience with the reference product in the marketplace.

It also must be kept in mind that the earliest date on which a FOB application can be submitted during an innovator's data exclusivity period should not be set so early that its final approval, upon expiration of the innovator's exclusivity, is so remote in time that the data on which it relies have become inapposite to the final FOB product due to, for example, subsequent changes to the FOB process technology used in commercial manufacturing. Finally, the likelihood that any

given FOB application would be approvable will be lower than it is today for generic drug applications, and the possibility that the Secretary may require additional clinical studies is greater. Thus, patent litigation would be premature if it were allowed to commence before a determination that the FOB application in question is complete and in condition for review without additional clinical studies.

A focus on triggering "patent challenges" at the earliest possible opportunity, possibly complemented by valuable regulatory exclusivity incentives for doing so, could thus lead to premature litigation as well as premature submission of FOB applications. The focus should be on incentivizing the timely submission of complete, high-quality, approvable FOB applications, not to reward the first "patent challenge." Experience under the Hatch Waxman Act confirms that incentives for early resolution of patent disputes must be crafted carefully to avoid unintended consequences. Premature litigation, both with respect to timing and with respect to the merits, is commonplace today in the small molecule space. For example, a survey of active NDAs for New Molecular Entities (NMEs) approved after March 2000 for which a paragraph IV certification could have been submitted after March 2004[37] shows that about 42% of all NMEs in this sample faced a paragraph IV challenge between the fourth and the seventh year following NDA approval (average 4.6 years). This, it is submitted, is an extraordinarily high litigation burden on both innovators and generic drug applicants that should not occur within just a few years after NME launch, and need not occur at all under a FOBs regime. A rational FOB framework would instead create incentives for timely patent dispute resolution within the innovator's statutory exclusivity period, to proceed in parallel with the FOB approval process, and would account for judicial determinations of patent validity and infringement by making the approval of the FOB application effective on the date of patent expiration or expiration of the innovator's statutory exclusivity period, whichever occurs later.

B2. How long might the approval process for a follow-on biologic application take? What factors might influence this timing?

It has been estimated that the time required for follow-on biologic manufacturers to obtain regulatory approval likely will be three to five years for pre-clinical and clinical testing, and one-and-a-half to two years for FDA review and approval.[38] Note that it also takes four to six years to bring manufacturing capacity on-line (likely developed concurrently with product development schedule).

Following passage of any legislation, FDA will need to create a regulatory scheme, testing requirements, and product-class guidelines. However, we note that, in most cases, the European Union has completed product-group-specific guidance in 12-18 months. While FDA must conduct its own guidance development process, it will have the benefit of what has been and can be learned from the European Union and, in some cases, this may allow FDA to complete guidance in a shorter time. Furthermore, there are administrative processes FDA will have to put

[37] The time for which Paragraph IV certification dates are available from the FDA at http://www.fda.gov/cder/ogd/ppiv.htm

[38] Grabowski, Henry, *et al*. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf

in place prior to approval of follow-on biologics; these will be separate from any guidance requirement. A guidance requirement would run concurrently with the establishment of these processes and thus would not create any additional delay.

B3. How might differences between patent portfolios for small molecule drugs and biologics affect patent litigation involving follow-on biologics? How long might patent litigation involving a follow-on biologic product take?

Compared to patent litigation under the Hatch-Waxman Act, biologics process patents would be expected to play a more prominent role in conjunction with other patents in the portfolio that protect the reference product. The main differences in the way in which patents would be litigated would, however, not be grounded in portfolio complexity, but in the way small molecule and biologics patent portfolios operate under different approval standards for generic drugs and FOBs. For example, because the reference product and the follow-on product would likely not need to be identical, there would be more frequent litigation of questions of noninfringement, doctrine of equivalents, and prosecution history estoppel. Claim construction would therefore be an even more important aspect of follow-on biologics patent litigation. In addition, it can be expected that the affirmative defenses of patent invalidity and unenforceability would be asserted at the same frequency at which they today occur during Hatch-Waxman litigation.

In another distinction from Hatch-Waxman litigation, biologics patent portfolios do not lend themselves to an Orange Book listing process of the kind relied on as the starting point for generic drug litigation today. Because a FOB product would likely not need to be the same as the reference biologic, and would invariably be made by a different manufacturing process, the innovator should not be forced to "guess" which of its product or process patents would probably cover a future FOB product and which ones might not, with potentially dire consequences for having guessed wrong. Instead, a mechanism that provides confidential access to follow-on product and process data for the sole purpose of identifying relevant patents would seem to be a more rational and practical approach.

Additional questions arise with respect to third parties who are likely to get involved in FOB patent litigation. Patent owners (such as university licensors) who have licensed relevant patents to the reference product sponsor, but who have reserved their patent enforcement rights, may need to be included in the patent resolution process. Early inclusion of such third party plaintiffs would seem to be necessary for a patent resolution process that provides legal certainty for innovators, patent holders, FOB applicants, and market participants prior to marketing of a FOB product.

It is not clear, however, that a relatively high degree of complexity of biologics patent portfolios, or the inclusion of third party patentees, would necessarily translate into a higher rate of litigation, or length of litigation, in the FOBs context. Industry experience over more than two decades of biotechnology patent litigation has shown that, while litigation involving biologic products can indeed be complex, such litigation has not been vastly more complicated than other high-stakes commercial litigation over other valuable products. Biotechnology patent disputes today can be adjudicated within a relatively stable doctrinal framework that is expected to

solidify further as biotechnology matures both as a science and as an industry. Further, some of the aspects that add complexity to biologics patent estates would not necessarily all come to bear in FOBs patent litigation. For example, composition-of-matter patents claiming the DNA that encodes the biologic protein, the host cell used for making it, or the promoter sequence used to drive its expression, etc., may not be relevant in U.S. patent litigation if the follow-on product is imported from India, China, or Europe. Third, the sheer rate of litigation per reference product is likely to be lower for biologics than it is for small molecule drugs. In the Hatch-Waxman context, a single reference product can get involved in multiple patent infringement suits against eight or more generic drug applicants.[39] Due to the complexities and cost inherent in developing biologic products, including FOBs, the number of potential FOB competitors – and the amount of litigation over multiple follow-on applications all referencing the same innovator product – will likely be smaller overall for at least a number of years. Finally, the length of reference product data exclusivity will be an important determinant of the numbers of "relevant" patents, because only patents that have a term longer than the reference product data protection would need to be adjudicated. It stands to reason that substantial periods of reference product data exclusivity would have the beneficial, if incidental, effect of simplifying litigation by taking those patents that expire during the innovator's data exclusivity period "off the table."

No good predictions can be made with respect to length of litigation. Patent litigation length depends on many factors that are highly specific to the parties, the legal issues in the case, the caseload of the court where the action was brought, the way the case is managed by the court, the individual judge to whom the case was assigned, and the like. To be sure, patent litigation generally does consume a lot of time. Experience from the small molecule sector, for example, suggests that the 30-month period envisioned by the Hatch-Waxman Act is not always sufficient to fully litigate a patent case on the merits. In any event, substantial reference product data exclusivity periods would likely be helpful in providing a litigation timeframe in which all key patent disputes could play out prior to FOB approval.

B4. When is it in the interest of a referenced biologic drug manufacturer to resolve patent issues prior to marketing by a follow-on applicant? When is it in the interest of a follow-on biologic applicant to resolve patent issues prior to marketing its follow-on biologic? When is it in the interest of either party to resolve patent issues following commercial marketing of the follow-on product?

For the reasons stated in BIO's answer to Question #1 in the patent section above, both innovators and follow-on applicants would normally be expected to want to resolve patent disputes prior to launch of the FOB. For a more complete discussion of the disadvantages of a process that routinely envisions patent resolution after FOB launch, see BIO's answer to Question #1 in the patent section as well.

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[39] See, e.g., multiple infringement actions filed on August 12, 2008 by Hoffmann-La Roche, Inc. against Cobalt Pharmaceuticals Inc., 2:08-cv-04054; Gate Pharmaceuticals**,** 2:08-cv-04058; Mutual Pharmaceutical Company, Inc. 2:08-cv-04060; Genpharm Inc. 2:08-cv-04052; Teva Pharmaceuticals USA, Inc. 2:08-cv-04059; Orchid Chemicals & Pharmaceuticals Ltd. 2:08-cv-04051; Apotex Inc. 2:08-cv-04053; Dr. Reddy's Laboratories, Ltd. 2:08-cv-04055; in the U.S. District Court for the District of New Jersey relating to defendants' Paragraph IV certifications as part of ANDAs to manufacture generic versions of Roche's Boniva® (ibandronate sodium) once-monthly tablets.

B5. What are the legal impediments facing a follow-on biologic applicant that has not been sued for infringement to obtaining a declaratory judgment on patent infringement or invalidity issues prior to commercial marketing of its follow-on product?

Appropriate follow-on biologics legislation would provide opportunities for innovators to protect their intellectual property rights – and for both parties to resolve disputes over them – before the FDA allows a follow-on product on the market. By making the filing of a FOB application an act of infringement, innovators and patentees would have a cause of action for infringement. Likewise, FOB applicants who have a justiciable case or controversy could seek legal and business certainty under the available Article III jurisdiction, as interpreted by the Supreme Court and the U.S. Court of Appeals for the Federal Circuit. By ensuring that these two complementary mechanisms would operate during the innovator's statutory exclusivity period, patents that claim the FOB product could be tested in litigation, thus ensuring patent and business certainty for the FOB applicant and innovator, and market certainty for patients, providers, and payers.

B6. Are regulatory exclusivities needed to encourage follow-on biologic applicants to challenge patents? Why or why not?

The emphasis should not and need not be on "challenging patents." The 180-day exclusivity under the Hatch-Waxman Act was designed to incentivize generic drug applicants to take on the cost of patent litigation because of free-rider concerns over other generic drug applicants that would benefit from this litigation investment. While it can fairly be asked whether the benefit of being able to exclusively market a first generic drug without significant price erosion for six months is commensurate with the cost of patent litigation,[40] many believe that the 180-day exclusivity has created an unnecessarily litigious environment by placing a high premium on bringing the earliest possible patent challenge, often by multiple filers who cannot afford to cede valuable generic exclusivity for a profitable drug to their generic competitors. 180-day exclusivity rewards the earliest possible challenge, not the one with the highest merits. In BIO's view, the award of regulatory exclusivity or similarly powerful incentives merely for "challenging patents" carries a significant risk of operating in multiple unintended ways that, in the Hatch-Waxman context, have already led to significant litigation, regulatory scrutiny, and legislative intervention.

BIO cautions against the creation of such misguided and unwise patent litigation incentives. FOB legislation should encourage and facilitate investment in bringing FOB products to market rather than "challenging patents." The logic for creating special patent challenge incentives under the Hatch-Waxman Act does not apply to FOBs because no two biologic drugs made by different manufacturers using different processes will be identical. Therefore, patent litigation over one FOB product will not necessarily apply to another FOB product, and the risk of

[40] This question can even more squarely be posed in light of the MMA Amendments of 2003, which confer 180-day exclusivity for the mere first filing of a paragraph IV certification, regardless of whether litigation ensues.

litigation free-riders faced in the generic context will be much diminished under a FOB framework.

Further, compared to a generic drug submission, the data package that will need to be assembled for a follow-on biologic application will be much more comprehensive and expensive. Also, regulatory approval of a follow-on biologic application will likely be less certain than it is for an average generic drug application, and further investment may be necessary to conduct any additional studies the Secretary may require, whether pre- or post-approval. In short, having made a very significant investment in its follow-on biologic technology, a follow-on applicant will be sufficiently motivated to challenge any patent barriers to entry even in the absence of artificial "patent challenge" incentives.

While it is thus unlikely that FOB applicants need special incentives to challenge patents, if Congress were to decide that a special regulatory exclusivity incentive is appropriate, the conditions under which such exclusivity would be triggered or forfeited would need to be carefully defined. In any case, such incentives should be designed to stimulate investment in FOB development and the submission of quality, approvable FOB applications, not the submission of naked patent challenges at the earliest possible opportunity.

Conclusion:

BIO appreciates this opportunity to respond to FTC's questions regarding competition provided by developing a regulatory approval pathway for follow-on biologic drugs. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

John M. Taylor, III
Executive Vice President, Health
Biotechnology Industry Organization

Attachment B

A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY[1] WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES

BIO recognizes the importance of providing the fruits of science and innovation in healthcare for the benefit of all American citizens. BIO represents both small and large biotechnology companies: some with products already on the market and most with their lead products still at the development stage with many years ahead of them before they can expect marketing approval. BIO's goals are to ensure that those companies with approved products are able to receive an appropriate return on their investment, and that the development stage companies can continue to finance their operations through accessing the venture and equity markets with the opportunity for an appropriate return in the future. This enormous reservoir of innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients.

Central to achieving these goals, any statutory pathway for follow-on biologic products ("FOBs") must establish a substantial period of data exclusivity to preserve incentives for research, development, manufacture, and approval of new biologic therapies. This is necessary because, under a statutory framework allowing for FOBs, there is a very real potential that the manufacturer of a FOB may be able to secure abbreviated regulatory approval based at least in part on the innovator's prior approval, and, at the same time, avoid infringing patents that protect the innovator's biotech product. That likelihood exists because of the confluence of two critical factors not present in the Hatch-Waxman construct for generic small molecule drugs. First, unlike a generic drug which must be the same as an innovator product, a FOB will only be required to be "similar' or "highly similar" to the corresponding innovator product. Second, because of the nature of biologic products – large molecules produced by living cells and organisms – patent protection is often narrower and easier to "design around" than that afforded to small molecule drugs.

In light of this potential gap in patent protection for biologics, data exclusivity in a FOB regime must be substantially longer than the five years currently afforded to drugs under the Hatch-Waxman Act. Biotechnology companies must have some certainty that they can protect their investment in the development of new breakthrough therapies for a substantial period of time in order to secure the necessary resources from venture capital firms and other funding sources. As described below, that period should be no less than 14 years if biologics are to receive the same length of effective market protection as drugs, and thus avoid skewing investment away from higher risk biologics research and development. Indeed, in striking the appropriate balance, Congress should err on the side

[1] Definition of data exclusivity: the time period after approval of the innovator's product during which the FDA may not approve a follow-on biologic product relying to any degree on the safety and effectiveness of the innovator product.

of protecting incentives for biomedical innovation because, as compared to the broader pharmaceutical industry, the biotechnology industry is largely comprised of small companies that are, for many reasons discussed herein, more vulnerable to changes in investment incentives.

The Need for Substantial Data Exclusivity for Innovator Biologics in any FOB Statutory Scheme

The Problem: The Similarity Standard for FOBs Creates a Gap that May Allow for Regulatory Approval without Adequate Patent Protection

Under the 1984 Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, a generic version of a small molecule drug may be approved for marketing only if its active ingredient is the "same" as in the innovator product. Thus, the patents that cover the innovator's drug molecule necessarily apply to the duplicate, generic version, and a generic may not enter the market until the innovator's patent expires. Indeed, the manufacturer of a generic drug may not have it both ways – it cannot gain FDA approval of its product by demonstrating that the active ingredient is the same as the innovator product and then turn around and claim in the patent context that its product is different from the innovator's drug. In this respect, the Hatch-Waxman exclusivity provisions work in concert with the patent system to provide market protection to innovator drugs.

In contrast, under the statutory framework being considered for FOBs, the same level of protection will not be available to innovator biological products. Unlike a small molecule generic drug, a FOB will not be required to be the "same" as the innovator product. Instead, it will only have to be "highly similar" to the innovator product. While the meaning of "highly similar" may vary between legislative proposals, there is no question that it falls short of the degree of sameness required of generic drugs. In fact, under one current legislative proposal, "highly similar" is defined in a manner that would allow for approval of FOBs with potentially significant differences from the innovator product. As a result, a FOB may be sufficiently similar to the innovator biologic to rely to some degree on the safety and effectiveness of the innovator product and thus receive abbreviated regulatory approval. Yet, it may still be different enough from the innovator product to avoid a patent infringement claim and, thus, get on the market well in advance of innovator patent expiration – undermining incentives to invest in innovation. The pace of medical advancement and the patients who stand to benefit from it would likewise suffer.

The Gap in Protection for Innovator Biologics Will Widen as Patent Law Yields Increasingly Narrow Patent Claims

Because of the nature of biologic products – produced by living cells and organisms – patent protection is different from and may be weaker than that afforded to small medicinal molecules.[2] First, because of current limitations of patentability of naturally

[2] This is so because the so-called "utility," "written description," and "enablement" requirements of the Patent Act are interpreted more stringently for biotechnology inventions than for most other technologies.

occurring substances, many biologics are protected only by process patents that may be easier to "design around." Moreover, under rules of patentability specific to biotechnology inventions, patent claims on biologics must often be narrowly drawn to the specific innovative aspect (e.g., a specific protein or nucleotide sequence) to be allowable. By contrast, patents on small medicinal molecules can often claim a whole class (a so-called genus) of related molecular structures and thereby provide a "penumbra" of patent protection covering the innovator small molecule.

These distinctions in patent protection for biologics are especially significant because, through a series of court decisions, the patent law is leading inexorably to narrower allowable claims. While this trend impacts all products, it is especially relevant to questions surrounding protection of innovator biologics in a FOB regime. That is because narrower patent claims for such products will result in a wider gap through which a FOB may be able to receive regulatory approval while still eluding an innovator's patents.[3] Furthermore, the sheer size of biologic products – often several hundred- or thousand-fold larger than small molecule drugs – increases the number of possible ways of altering the product such that it would be similar enough to the original product to qualify as a FOB but different enough to be outside the scope of the patents on the original product. Disputes over patent claim coverage that are likely to arise from this situation would lead to an increase in litigation expenses and add to the uncertainty that biotechnology companies could protect their investment.

Strong Data Exclusivity Will Preserve the Balance that Congress Found Necessary to Stimulate Innovation in the Pharmaceutical Industry

With passage of the Hatch-Waxman Amendments in 1984, Congress recognized that normal patent protection alone is insufficient to provide small molecule pharmaceutical innovators with sufficient market exclusivity to allow them to recoup clinical research and development costs. To address this problem, Congress established a period of data exclusivity for drugs, and it created a mechanism allowing for the extension of patents on innovator drugs and biologics for up to 14 years following approval of the product.[4] In providing for patent extensions of up to 14 years, Congress acknowledged that – unlike most other industries – the pharmaceutical industry rarely benefited from the full length of normal patent protection (then 17 years) due to the long development and regulatory approval process for drugs. Given that Congress has previously concluded that 14 years of patent protection is appropriate for drugs and biological products, any statutory

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Moreover, patents cannot claim something that occurs naturally. Therefore, because many biotech products are "artificial" (recombinant) versions of naturally occurring proteins, the patent claims must be narrowly crafted (i.e., limited to specific isolated and purified DNA sequences, proteins, or clonal cell lines) in order to avoid encompassing naturally produced molecules. In contrast, most of the small medicinal molecules are synthetic. It is in part because they never existed before in nature that the claims to such synthetic small molecules may be drafted more broadly than claims to biotechnology products.

[3] Manheim, Granahan, and Dow. "'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry," Health Affairs, March/April 2006.

[4] Extension is calculated by taking: ½ of the time spent diligently from IND effective date to NDA submission; and the full NDA review period; patents cannot be extended by more than 5 years. The patent extension also cannot result in a patent that has a term of more than 14 years post-NDA approval.

formula that allows for FOBs should at least guarantee that same degree of effective market protection – and, for the reasons discussed above, that protection can be accomplished most predictably through data exclusivity.

The presence of substantial data exclusivity also would serve as an additional incentive to research and prove the safety and effectiveness of new indications for existing biologics. Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time. It is important to provide substantial exclusivity for the original treatment in order to support the expensive further development for these later indications, as well as an additional period of exclusivity – no less than two years beyond the standard 14 year period – to provide the proper incentives to research and bring to market the vibrant pipeline of treatments that can allow cancer patients to live longer and healthier lives.

It also is important to note that this length of data exclusivity for innovators in any FOBs regime would not operate as an extension of exclusivity. Rather, the period of data exclusivity would run concurrently with the patent term for the product, which itself may run at least 14 years. Data exclusivity would create actual market protection for the innovator product only in those instances where the follow-on manufacturer is able to work around the patents held by the innovator but still gain approval of its product as a follow-on. In this respect, a 14-year period of data exclusivity serves essentially as an insurance policy that provides the innovator with some certainty of protection, given that a FOB can be approved on the basis of a less stringent standard of similarity. Thus, 14 years of data exclusivity is an essential component of a balanced statutory pathway for FOBs, making possible their introduction and use in the market while appropriately safeguarding incentives for biotechnology innovation.

Empirical Data Support a 14-Year Period of Data Exclusivity for Biologics

In 1998, the Congressional Budget Office found that the average period of time for marketing of a drug product with patent protection is 11½ years[5], and new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.[6] Further, the breakeven point for a biologic occurs after it has been on the market between 12.9 and 16.2 years.[7] As described below in more detail, biotechnology companies bear enormous costs and risk to develop life saving products. As a result, it is essential that the period of effective market protection for drugs – 14 years – be extended to biologics. Indeed, if the data exclusivity period for biologics is less than that, then, because of the higher risks of biologics development, it will skew investment options away from biotechnology.

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[5] Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, "The Effects of the Hatch-Waxman Act on the Returns from Innovation."

[6] Grabowski, Henry and Margaret Kyle. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," Managerial and Decision Economics (*forthcoming)*.

[7] Grabowski, Henry. "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper. June 2007.

Strong Protection for Innovative Biologic Products Is an Essential Incentive for Investment in Biomedical Innovation

In crafting a FOBs regime, it is important to err on the side of incentivizing innovation due to the unique elements of the biotechnology industry, which is largely comprised of small, privately-funded start-up companies without reliable revenue streams. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted FOBs regime.

Biotechnology Companies Bear Enormous Costs and High Uncertainty

- Cost of Capital: The cost of capital for small biotechnology companies is much higher than the cost of capital for large pharmaceutical firms. While large pharmaceutical companies have product revenue streams that they reinvest in the research and development of new pharmaceuticals, the vast majority of biotechnology companies, as shown below, do not have any marketed products and have very limited revenues.

  The lack of a product revenue stream coupled with risk of early product development drives up biotechnology companies' cost of capital:

  - Whereas the cost of capital for a large pharmaceutical company averages 15.7%, biotechnology companies with at least one drug approved have an average cost of capital of 18.7%
  - Biotechnology companies with only a drug candidate in clinical phase II or III trials have a cost of capital averaging 27.4%.[8]

  The higher cost of capital coupled with failure to give an adequate data exclusivity period to biotech products could result in shifting investment away from small, innovative biotechnology companies.

- Production Costs: Biologics, as opposed to pharmaceuticals, are produced using biologic processes such as cell cultures or fermentation and are then purified. Indeed, cell culture facilities:

  - Take on average three to five years to construct
  - Cost between $250 million and $450 million
  - Must often be constructed before drugs enter clinical testing[9]

[8] Grossmann, Martin. Entrepreneurship in Biotechnology, Physica-Verlag NewYork, 2003.
[9] Grabowski, Henry, Iain Cockburn and Genia Long. "The Market for Follow-On Biologics: How Will It Evolve?" Health Affairs, 25(5).

Further, the cost of materials to produce a biologic is 20 to 100 times more than the materials used to produce a small molecule pharmaceutical.[10]

- Manufacturing Uncertainties: Biologics manufacturing necessitates far more planning, investment and skilled personnel and, thus, can be much riskier than small-molecule manufacturing.[11] "A typical manufacturing process for a chemical drug might contain 40-50 critical tests. The typical process for a biologic, however, might contain 250 or more critical tests…Consequently, construction and validation of new facilities is disproportionately expensive and time-consuming."[12]

- Late-Stage Failures: The success rate for late-stage biotechnology products is lower than for pharmaceuticals. From 2001 – 2005, the success rate of a Phase III trial for the average pharmaceutical was 65% to 75%; whereas, the success rate of a Phase III trial for biotechnology produces was 54% to 58%.[13] These failures occur at the last stage of product development – after years of research and hundreds of millions of dollars have been spent.

The Biotechnology Industry is Comprised Mostly of Small, Start-ups

The biotechnology industry in the U.S. is still relatively nascent: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies—many of which will never see a product come to market or turn a profit—that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology companies (all biotechnology companies but the top ten) account for two-thirds of the industry's clinical pipeline.*[14]

The statistics speak to the challenges this emerging industry faces: in 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:[15,16]

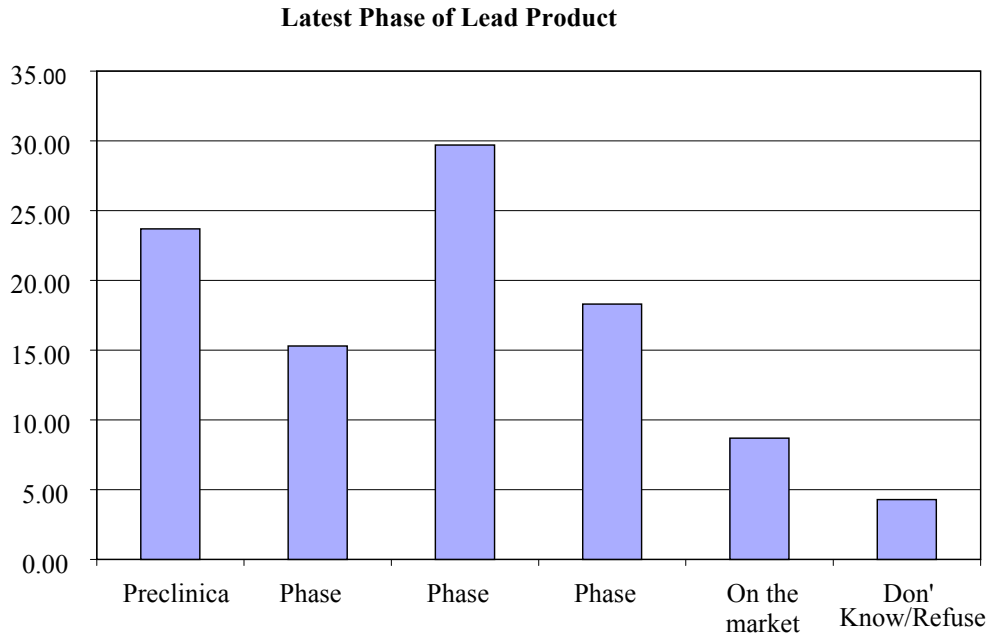
Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
$B Net Loss	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	4.1

[10] U.S. Bancorp Piper Jaffrey. "The Road Ahead for Biologics Manufacturing," January 1, 2002.
[11] Lakshmikanthan, Jayant. "Outsourcing: Biologics Manufacturing: The CMO Advantage," International BioPharm, Feb. 1, 2007.
[12] Webster, Christopher, et al. "Can There Be an Abbreviated Applications, Generics or Follow-On Products?" BioPharm International, July 2003.
[13] Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.
[14] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.
[15] Ernst and Young LLP, Annual biotechnology industry reports, 1995 – 2006. Financial data based primarily on fiscal-year financial statements of publicly traded companies.
[16] Only about 20 biotech companies are currently profitable: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

A 2006 Biotechnology Industry Organization (BIO) representative survey of 300 small biotech companies showed:

- **Company Size:** 65% of the companies surveyed have fewer than 50 employees. 40% of the respondents reported that their company's revenue from all sources was less than $150,000 in the previous year, and 66% had revenues under $1 million annually. Additionally, of those companies that do have revenue, the only revenue streams for the vast majority of the companies were milestone and royalty payments.

- **Product Development:** Of the companies surveyed, less than 10% have a product on the market. The chart below shows the distribution of latest phase of lead product development, which represents each individual company's most fully developed product:



Thus, while the biotechnology industry continues to grow and expand, the vast majority are emerging enterprises, relying on the investment community and the talents of their dedicated employees to bring much-needed treatments to fruition. Failure to provide substantial data exclusivity could fundamentally alter the ability of these small companies to continue to innovate.

U.S. Public Policy Should Encourage a Growing Biotechnology Industry

The U.S. leads the world in biotechnology innovation:

	U.S.	Europe	Canada	Australia

Annual R&D	$18.5 B	$4.2B	$1.7 B	$1.0 B
No. of Companies	1,473	1,878	470	226
No. of Public Companies	363	96	81	58
No. of Employees	146,100	32,470	7,440	6,393

Source: Burrill & Company, Ernst & Young

Indeed, the per capita biotechnology R&D is 574% higher in the U.S. than in the European Union.[17] U.S. public policy thus should support this important U.S. industry and employer and encourage its growth through effective market protection from unfair and premature competition by generic companies. Only in this way will the U.S. continue to lead the world in biotechnology innovation.

Conclusion

Continued U.S. leadership in biotechnology innovation, made possible through sound public policy as outlined here, will enable further progress in the research and discovery of breakthrough therapies to improve the health and lives of patients across the globe. Today, as the legislative framework for follow-on biologics comes into view, it is critical that data exclusivity of no less than 14-years be included as a central component of that framework, given the uncertainties of effective patent-based protection and the higher risks associated with investment in biotechnology.

[17] Based on EU's population of approximately 457 million people and the U.S. population of 298 million people – both figures estimated in July 2006.

Attachment C

Data Exclusivity Periods for Biologics:

Updating Prior Analyses and Responding to Critiques

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I. SUMMARY

Recent discussion, including at the November 21, 2008 Federal Trade Commission Roundtable on Follow-on Biologic Drugs, has addressed the question of the appropriate duration of data exclusivity (also called data protection) for innovative biologics. This paper proposes that the breakeven financial analysis outlined in an earlier paper is an appropriate framework for the assessment of different data exclusivity periods being proposed in the context of an abbreviated regulatory approval pathway for biosimilars.[1] Among the key parameters in this model are: the cost of capital;[2] expected margins produced by marketed biotech products (contribution margin);[3] and other financial parameters such as required pre-marketing and post-marketing R&D investments. Applying this model led to the conclusion that a representative portfolio of biologics would "break even" or just cover its costs of development, manufacturing and sales, together with the industry's cost of capital, in 12.9 to 16.2 years, thereby providing support for a substantial data exclusivity period.

A recent critique, which adopts the same model and framework for its assessment of the appropriate duration of data exclusivity periods, suggests that alternative values for the cost of capital and contribution margin parameters are more appropriate and that, applying them

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[1] Grabowski, H., "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Reviews Drug Discovery*, 7, 479 – 488 (2008).

[2] The cost of capital is the annual rate of return that an investor would require on average in order to make a given investment. In the case of biologics, this accounts for the risks associated with potential failure to develop or market the biologic candidate product successfully.

[3] The contribution margin is a measure of how much a company earns in sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative expenses. Contribution margin is not equivalent to profit margin, which also subtracts the costs of R&D, and interest, taxes and all other expense items.

supports a lower breakeven period, and therefore, a lower data exclusivity period.[4] It also considers the effects on breakeven periods of different assumptions for innovator product share and price impacts resulting from biosimilar entry. This paper corrects computational problems and inconsistencies in Brill's critique of the breakeven period. Furthermore, it disputes his claim that a 10% cost of capital and an average 60% contribution margin assumption are reasonable and appropriate baseline valves, and performs a number of sensitivity analyses using a range of input values. Together, these analyses suggest that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period, under reasonable assumptions.

The remainder of this paper is organized as follows:

- **Section II** discusses the importance of data exclusivity to biologics, including why patents alone may be insufficient to provide protection for biologics;
- **Section III** summarizes why the portfolio cash flow approach adopted in this paper is an appropriate framework for analysis of the impact of data exclusivity limits on investment and competition in the biotech industry;
- **Section IV** summarizes the key points in a recent critique of the previous "breakeven" analysis published in *Nature Reviews Drug Discovery* (hereafter referred to as the *Nature* model) and identifies four problems and implausible assumptions in this critique;
- **Sections V and VI** refute key assumptions from this critique, including the a cost of capital that is too low (Section V) and contribution margins that are too high (Section VI);
- **Section VII** notes that the critique fails to take into account other countervailing assumptions in the prior *Nature* analysis that tend to understate expected breakeven periods;
- **Section VIII** extends the previous *Nature* analysis to incorporate other impacts associated with biosimilar entry, and summarizes the results of sensitivity analyses on the extended model;
- **Section IX** summarizes the overall results of the additional analysis in this paper; and
- A brief **Appendix** addresses the critique's computational inconsistencies

[4] Brill, A., "Proper Duration of Data Exclusivity for Generic Biologics: A Critique," unpublished manuscript, November 2008.

II. THE IMPORTANCE OF DATA EXCLUSIVITY TO BIOLOGICS

Data exclusivity is the period of time between FDA approval and the point at which an abbreviated filing for a biosimilar relying in whole or in part on the innovator's data on safety and efficacy can receive final approval. Data exclusivity is designed to preserve innovation incentives, and recognize the long, costly, and risky process necessary for the innovator to gain FDA approval. Data exclusivity is a critical issue for the future of biologics, with different provisions for data exclusivity in recent legislative proposals ranging from zero to 14 years. All bills other than H.R. 1038, sponsored by Representative Henry Waxman of California, proposed combined periods of at least 12 years.[5, 6]

Data exclusivity periods are essential to compensate for some important shortcomings in patent protection for biologics. Data exclusivity extends from the date of product approval, and this protection period runs concurrently with any remaining patent term protection for the biologic. That is to say, data exclusivity provides additional protection to the innovator when the remaining patent length is shorter than the data exclusivity period at the time of approval (which can occur due to lengthy preclinical and clinical research required to obtain FDA approval), or to

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[5] Although H.R. 1038 contains no data exclusivity period at all, its absence did not necessarily indicate opposition to a provision, according to coverage at the time, but rather a desire to hold off on backing a specific figure until more was learned about what an appropriate period should be. See summary in *Inside Health Policy,* "Boston University Study Criticizes Exclusivity Measures in Biogenerics Bills," September 30, 2008. Access October 29, 2008 at www.insidehealthpolicy.com/secure/health_docnum.asp?f=health_2001.ask&docnum=9302008_boston&DOCID=9302008_boston.

[6] Recent legislative proposals for establishing an abbreviated pathway for biosimilar entry consider both permissible filing dates and overall market protection periods. For example, the bill S.1695, sponsored by Senator Kennedy, allows for four years before an abbreviated filing can occur, during which the FDA cannot rely on innovator's data on safety and efficacy to review an abbreviated biosimilar application, followed by an additional eight years during which FDA review of the application can take place but the application cannot be approved, for a total of 12 years of data exclusivity.

the extent that the patent is circumvented by a biosimilar prior to its expiry. Patent protection alone may be insufficient for biologics in the context of biosimilars for two primary reasons:

(1) The standard for FDA approval of biosimilars is likely to be based on *similarity* rather than *sameness*, allowing for greater differences between the biosimilar and the reference product than are allowed between an AB-rated generic small-molecule drug and its reference product. As a result, development of a biosimilar may allow for greater deviations from the reference product and greater opportunity to deviate slightly from the patented technology, thereby sidestepping patent infringement while still benefiting from an abbreviated FDA application process. In 2007 remarks before the Committee on Oversight and Government Reform, Dr. Janet Woodcock of FDA noted, "Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product."[7]

(2) Patents for biologics, unlike for small-molecule drugs, do not typically protect the entire molecule or class of related molecular structures. Biologics are much more complex than small-molecule drugs, and the patents protecting biologics tend to focus on certain aspects of the protein or ways of producing the protein rather than on protecting the entire molecule.[8]

Data exclusivity provides investors with an "insurance policy" against the potential failings of patent protection for biologics. Recent evidence suggests that the effective marketing

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[7] Woodcock, J. "Follow-on Protein Products" Statement before the Committee on Oversight and Government Reform, U.S. House of Representatives, 26 March 2007, FDA web site (online), http://www.fda.gov/ols/2007/rotein32607.html, (2007).

[8] Manheim, H., Granaham, P., and Dow, K., "Follow-on Biologics: Ensuring Continued Innovation in the Biotechnology Industry," Health Affairs, 25:394-404 (2006).

exclusivity period for small-molecule drugs (the time between launch and first generic entry) is approximately 12 years on average.[9] Data exclusivity for small-molecule drugs is generally not the constraint on generic entry (although in recent years, it has become increasingly important for small molecules due to the rise of Paragraph IV challenges under the Hatch-Waxman Act), whereas it is expected to be more determinative for biologics due to the nature of their patent protection.[10]

III. A PORTFOLIO DISCOUNTED CASH FLOW APPROACH IS AN APPROPRIATE FRAMEWORK FOR ANALYSIS OF THE IMPACT OF DATA EXCLUSIVITY LIMITS ON INVESTMENT AND COMPETITION IN THE BIOTECH INDUSTRY

In evaluating the impact of data exclusivity periods of different durations on the incentives for innovation, an appropriate perspective to adopt is that of a potential investor who weighs alternative investments, together with their expected risks, costs and returns. Venture capital and private equity are the primary sources of early stage investment in biotech start-ups, which account for many new pipeline biologics. Venture capital-backed firms constitute 40 percent of employment in biotechnology.[11] Such investors account for the low probabilities of success of any individual opportunity by investing in a long-term portfolio of opportunities, most of which ultimately will not succeed, but one or two of which may earn significant returns years later. Larger established firms, as well as venture investors, need to take a portfolio approach,

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[9] Grabowski, H. and Kyle, M., "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics*, 28: 491-502 (2007). For drugs with first-generic entry in 2005, the average market exclusivity period (MEP; the time between product launch and first-generic entry) was 11.5 years (drugs with sales greater than $100 million) to 13.0 years (all drugs).

[10] Grabowski, H. "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents, and Political Pressures, *PharmacoEconomics*, Vol. 22, Suppl. 2, 2004, pp. 15-24.

[11] Lawton R. Burns, Michael G. Housman, and Charles A. Robinson, "Market Entry and Exit by Biotech and Device Companies Funded by Venture Capital," *Health Affairs* 28, no. 1 (2009): w76-w86.

given the low probability of success for new biological candidates, and the skewed distribution of sales revenues for approved marketed candidates. Venture capital firms use discount rates that vary by stage of investment, and account for a decreasing level of risk as products approach launch and commercialization. An empirical analysis of this issue found that discount rates vary from 70% down to 25%, depending on stage of finance (start-ups to IPOs).[12] Similarly, established biotech or pharmaceutical firms apply a portfolio approach to their selection of which candidate molecules to advance in development and to the valuation of licensing and acquisition opportunities, using a risk-adjusted cost of capital, as discussed below.

This approach was outlined in an article recently published in *Nature Reviews Drug Discovery* (Grabowski, 2008; henceforth referred to as the *Nature* article). In a recent unpublished white paper, Alex Brill utilizes the same framework to comment on the optimal data exclusivity period. Brill accepts the basic premise of the *Nature* article, namely that data exclusivity times should be guided by the time necessary for a representative new biological entity to just cover its expected R&D, sales and marketing investments, together with the industry-wide cost of capital. This is defined as the "breakeven lifetime" in the parlance of economics and financial studies.

Brill also accepts the appropriateness of a portfolio approach to evaluating R&D investment decisions, like the one performed in the analysis in the *Nature* article. Accordingly,

[12] Sahlman,W.A., "The Structure and Governance of Venture-Capital Organizations," *Journal of Financial Economics*, 27(1990) pp. 473-521, Table 6 at p. 511.

he also focuses on the returns for a representative biological product from a portfolio based on the historical distribution of R&D costs and revenues.[13]

IV. BRILL'S ANALYSIS

As discussed, the analysis presented in the 2008 *Nature* article results in breakeven returns for the representative biologic between 12.9 years and 16.2 years. This is depicted in Exhibit 1, which is Figure 7 from the *Nature* article. This diagram shows the cumulative net present values over a 30-year period from the beginning of the R&D investment period through market launch and over the product life cycle. As shown in this diagram, it takes 12.9 years after launch, at a discount value of 11.5%, for the cumulative net present value (NPV) to become positive in terms of value from cash flow, and 16.2 years for breakeven at a discount value of 12.5%. Alternatively stated, it takes 12.9 to 16.2 years for the firm to earn a rate of return which is just equal to its risk-based cost of capital.

A. DESCRIPTION OF BRILL'S ANALYSIS

In his white paper, Brill makes three changes from the analysis presented in the *Nature* article that affect the breakeven point calculation:

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[13] In particular, his basic inputs include average R&D investment from DiMasi and Grabowski, 2007 (DiMasi, J., and Grabowski, H., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, Vol. 28, Issue 4-5, pp. 469-479), sales revenue distribution for biologics based on Grabowski, 2003 (Patents and New Product Development in the Pharmaceuticals and Biotechnology Industries," *Science and Cents*, edited by John Duca, Federal Reserve Bank of Dallas, 2003, pp. 87-104), and post approval R&D costs and product launch expenditures based on Grabowski, Vernon and DiMasi, 2002 (Grabowski, H., Vernon, J., DiMasi, J., "Returns on Research and Development for 1990s new Drug Introductions," *Pharmacoeconomics*, Vol. 20, Supplement 3, 2002, pp. 11-29).

(1) First, he assumes that the innovator's product will retain a significant share of its pre-entry sales after the market entry of biosimilars, and bases his estimates in this regard on recent assumptions from the Congressional Budget Office (CBO).[14]

(2) Second, he utilizes a 10% baseline real cost of capital for the representative biotechnology firm, compared to the 11.5% to 12.5% range utilized in the *Nature* article.

(3) Third, he utilizes a 60% contribution margin for the representative biologic product, compared to a 50% baseline value in the *Nature* article.

The *Nature* article estimates a breakeven lifetime of between 12.9 and 16.2 years for the representative biological product. With the above changes in assumptions, Brill claims that relatively short exclusivity periods would still be compatible with significant innovation incentives. In particular, he claims that a seven-year data exclusivity period with subsequent biosimilar entry would still allow firms to break even in just over ten years.

However, Brill's analysis is subject to computational problems and inconsistencies, as well as implausible assumptions. When these are corrected and accounted for, his implication that short data exclusivity periods, coupled with rapid biosimilar entry, still provide strong innovation incentives is not valid. In this paper, we perform alternative sensitivity analyses on particular inputs and assumptions, and confirm the importance of a substantial data exclusivity period for biologics.

[14] Congressional Budget Office, Cost Estimate: S.1695 Biologics Price Competition and Innovation Act of 2007, June 25, 2008.

B. CRITIQUE OF BRILL'S ANALYSIS

Exhibit 2 is taken from Brill's white paper (it is Figure 3 in his paper and appears with results uncorrected). This exhibit uses the same framework as Exhibit 1, but reflects the changes Brill implemented to incorporate biosimilar entry (including his calculation errors and implausible assumptions). In particular, for the specific case presented in this exhibit, there is a hypothesized data exclusivity period of seven years, after which biosimilars are assumed to enter. Brill relies on a discussion of shares and prices from the CBO bill-scoring document to make assumptions on innovator share and price erosion following biosimilar entry. Brill assumes that, on average, biosimilars will capture a 10% share of the market in the first year of entry, growing to a steady state of 35% within 4 years. He further assumes that price (sales-weighted) would decline by 20% in the first year, and reach a steady state of a 40% price discount by the fourth year. The analysis is also performed under Brill's assumption of a 10% cost of capital and a 60% contribution margin. As shown by the dotted line in this diagram, Brill finds the firm can still break even in year 10, and earn increasingly positive cash flow values after that point.

The four problems and implausible assumptions in Brill's analysis are:

(1) ***Brill's calculations include a significant computational problem and inconsistency in incorporating assumptions made by the CBO in its scoring of follow-on biologics bill S. 1695 into the Nature model; correcting these problems does not yield his results as reported and does not support a seven year data exclusivity period.*** Since the publication of the *Nature* article, the CBO has published a bill-scoring estimate that includes some discussion of potential market shares and price discounts with biosimilar entry. Brill references the CBO discussion in his assumptions of biosimilar shares and price discounts, which

are used to evaluate whether particular data exclusivity periods are compatible with eventual breakeven returns. In doing so, however, the treatment of price discounts and margin changes in Brill's analysis are inconsistently incorporated into the investment returns model in the *Nature* article. This in turn results in a significant underestimation of breakeven times.

(2) ***Brill's assumption on the cost of capital is not reasonable and is at odds with most current best thinking on the subject and with other commonly used industry metrics***. Indeed, the most sophisticated analysis in the current literature, together with accepted published industry metrics, suggests real costs of capital for biotech firms are well above the 11.5% to 12.5% assumed in the *Nature* article. (Golec and Vernon, 2007; Ibbotston Annual Cost of Capital Yearbook, 2008)[15] Brill also fails to acknowledge the large subsample of private and public biotech firms without marketed products that need to rely on venture funding and financial instruments at very high costs of capital.

(3) ***Brill's assumption for the average contribution margin relies on results from six of the most profitable biotech firms, and fails to consider the high degree of variability in profits even among this small, upwardly biased sample. His approach also puts inordinate weights on two of the most successful biotech firms[16].*** As a result of these sample selection issues, his 60% margin can be viewed as being an extreme value, or upper bound, rather than being a plausible baseline value.

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[15] Golec, J., and Vernon, J., "Financial Risk in the Biotechnology Industry," *Journal of Applied Economics and Health Policy*, forthcoming; also NBER Working Paper # 13604, November 2007. Ibbotson, *Cost of Capital Yearbook*, Morningstar, 2008.

[16] Together, Amgen and Genentech alone receive 67 percent of the overall weights in Brill's calculation of the average.

(4) ***Brill ignores countervailing assumptions already reflected in the Nature article breakeven analysis, which have the effect of producing estimated breakeven periods that are shorter than likely actual breakeven periods***. For example, the representative portfolio modeled reflects the mean values observed for only the top four ranked quintiles of the sales distribution of established biotechnology drugs, with the bottom quintile excluded. Excluding all biologics in the lowest tail of the distribution biases breakeven periods downward. In addition, the *Nature* model assumes that firms can use existing plant assets to produce the biologics in the modeled portfolio at commercial scale and that capital costs are captured fully by depreciation charges subsumed in the contribution margin. This approach also biases breakeven periods downward, as some new plant construction or retrofitting would be required. The cost of a new multi-product manufacturing plant for large-scale commercial production is substantial. It has been estimated elsewhere that a new manufacturing plant can take three to five years to construction and can cost $250 million or more.[17] Even retrofitting existing plant assets can cost between $50 and $100 million. Finally, the *Nature* model assumes a 3.5% reduction in branded biologic share each year, beginning in the 10th year to account for therapy obsolescence. Vigorous dynamic competition in the therapeutic areas with high unmet need (such as rheumatoid arthritis, oncology and other areas) typically served by biologics, and the high numbers of pipeline products in these areas suggest actual rates of share attrition may be higher in the coming years.

[17] Molowa, D.T. The State of Biologics Manufacturing. J.P. Morgan Securities, Equity Research Healthcare Note. 16 February 2001.

C. CORRECTING LOGICAL INCONSISTENCIES IN BRILL'S ANALYSIS

Brill's first point concerning innovator sales after biosimilar entry can be viewed as a logical extension or sensitivity analysis to the breakeven analysis. In the *Nature* article, various qualifying points that had countervailing effects on the breakeven lifetime were presented.[18] One such qualifying point was that, for the foreseeable future, innovative firms may retain significant shares of the market after the entry of biosimilars. This is in contrast to the current experiences of small-molecule drugs, where as behavior under Hatch-Waxman has evolved over the years, high sales products now often lose 90 percent of the market to generics within just a few months (Grabowski, 2004; Silver, 2008).[19] Over time, the markets for biosimilars may evolve to more closely resemble the now intensely competitive ones for generic chemical entities (Grabowski, Cockburn and Long, 2006).[20] In the meantime, however, current biologics may be able to earn potentially significant revenues after biosimilar entry, prolonging the innovative product's life beyond the expiration of data exclusivity periods. Therefore the impact of innovator sales and price erosion on the breakeven calculation needs to be further investigated.

Brill's analysis of these issues, however, has inconsistently implemented how the price erosion assumption will affect the model results presented in the *Nature* article. In calculating changes in contribution margins, Brill assumes that the innovator will discount the price of the brand biologic in response to biosimilar entry, by the same amount as the sales weighted price of

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[18] Most of the other qualifying points in Grabowski (2008) operate in an opposing manner as discussed below, and these points were ignored by Brill.

[19] Grabowski, H., "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents and Political Pressures," *Pharmcoeconomics*, Vol. 22, Suppl. 2, 2004, pp. 15-24. Silver, R., "A Wall Street Perspective on Generics," 2007 GPhA Annual Meeting, March 1-3, 2007, available at http://www.gphaonline.org/AM/CM/ContentDisplay.cfm?ContentFileID=593.

[20] Grabowski, H., Cockburn, I., Long, G., "The Market for Follow-On Biologics: How Will it Evolve?," *Health Affairs*, 25, no. 5 (2006), pp. 1291-1301.

the biosimilar entrants. However, he fails to correspondingly reduce the level of assumed brand biologic sales in his modification to the model by the same price discount. This inconsistent computational approach means that he multiplies margins that take the price erosion assumptions into account by revenues that do not.[21]

As discussed in the sensitivity analysis later in this paper, Brill's interpretation of the CBO assumptions on the brand's price response is open to question. The CBO report states that biosimilar entry will constrain innovator prices, but does not specify by how much it will do so.[22] Hence, this is a subject for further sensitivity analysis that we undertake in Section VIII. In this section, however, we examine the effects of the logical inconsistency in Brill's analysis, given his interpretation that the innovator price will be the same as the sales weighted average of the biosimilars. Further details and an illustrative example of this computational problem are presented in the Appendix.

Correcting Brill's computational problems and inconsistencies has a substantial impact on his findings. Applying his overstated baseline profit margin assumption of 60% and understated baseline cost of capital assumption of 10% to the corrected model, and maintaining his assumption of a seven-year exclusivity period results in a breakeven period of over 13 years, not the just over 10 years that he reports. Furthermore, he erroneously states that even with a cost of capital of 11.5% and a seven-year exclusivity period (and his other assumptions

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[21] These issues are discussed more specifically in the Appendix to this paper. In the updated *Nature* model calculations presented in this paper, we assume that costs are reduced proportionately with reductions in output.

[22] In a telephone conversation on December 22nd, CBO confirmed that the appropriate interpretation of the assumption in their report that the availability of biosimilars will constrain brand-name prices is that brand-name prices will be lower than they would otherwise be without any biosimilar entry. However, the CBO has not released any quantitative assumptions in this regard and are still analyzing the issue in light of new information.

unchanged), a breakeven period (of unspecified magnitude) results. In fact, when his calculation error is corrected, there is no breakeven period in the first 50 years when applying an 11.5% cost of capital assumption and a seven-year breakeven period.[23]

D. SENSITIVITY OF BRILL'S RESULTS

After correcting for calculation problems and inconsistencies, Brill's findings are extremely sensitive to small changes in his assumptions. Exhibit 3 uses the same framework as Exhibit 2, but corrects for Brill's calculation error. Using reasonable assumptions, a seven-year exclusivity period is insufficient:

- Keeping all of his assumptions unchanged but reducing the margin assumption from 60% to 55% results in ***no breakeven period within the first 50 years***.
- Similarly, increasing just his cost of capital assumption from 10% to 11.5% (and keeping his margin assumption at 60%), again results in ***no breakeven period within the first 50 years***.

Even if Brill's margin and cost of capital assumptions were reasonable, which they are not, such high sensitivity in findings to small changes in those assumptions would be of significant concern.

It is also important to keep in mind that while biosimilar penetration rates and/or brand price discounts may be modest in the near term (as reflected in estimates for existing products by

[23] Whether or not a breakeven period exists beyond 50 years following launch of the brand was not investigated, as it is unlikely that investors will consider projects with such a lengthy term to break even regardless of the discount rate.

the CBO or others), they could very well exceed those assumed by Brill in the longer run.[24] Data exclusivity provisions are focused on innovation incentives for the long-term. Many of these molecules will not reach the market for a decade or more, and biosimilar entry will be even further removed in time from market launch. Over time, attrition rates may increase for biologics as the FDA develops a larger experience base, and private and public reimbursement systems evolve for biosimilars.

Even if one accepts Brill's cost of capital and contribution margin assumptions, increasingly aggressive biosimilar entry following the expiration of data exclusivity periods would result in longer breakeven periods over time or no breakeven period at all over a reasonable timeframe.

V. 10 PERCENT COST OF CAPITAL IS NOT CREDIBLE FOR BIOTECH FIRMS

The *Nature* article's estimates of the real cost of capital, 11.5% and 12.5%, are substantially below reliable broad industry estimates of the cost of capital for biotech R&D investments. These original estimates were based on a small group of biotech firms that had multiple FDA-approved biologics and a history of positive operating profits over the past decade, and understate cost of capital for the industry more broadly, which includes smaller biotech firms with few or no biologics on the market. As noted in the *Nature* article, for these reasons, the values used for the real cost of capital are conservative, meaning they are below those faced by most firms. In addition, recent best academic literature estimates the real cost of capital for

[24] The CBO's estimate focuses on a 10-year timeframe beginning with the present when the initial implementation of a regulatory pathway for biosimilars would be developed and implemented and the first biosimilars would enter the market.

biotechnology firms to be no lower than 13.25%, and in some cases much higher when the focus is small to mid-size biotechnology firms:

- Golec and Vernon (2007) estimate costs of capital for the biotechnology industry generally, relying on a three-factor Fama French model (as opposed to a CAPM model), which is the generally accepted, appropriate methodology for estimating cost of capital.[25] Golec and Vernon (2007) estimate a nominal cost of capital of 16.75% for biotech R&D investment, and Vernon recently noted that this corresponds to a real cost of capital of 13.25%, significantly higher than the 11.5% and 12.5% figures used in the *Nature* models.[26]
- Ibbotson's Cost of Capital 2008 Yearbook, a widely accepted general industry source for cost of capital estimates, reports a similar nominal three-factor Fama-French estimate of 17.49% for the median publicly-traded company within the biotechnology SIC code (2836). Assuming a 3% annual inflation rate, this figure would correspond to a 14.07% real cost of capital.

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[25] Fama-French three factor return models are considered to be far superior for estimating cost of capital in industries such as biotechnology. As noted in Golec and Vernon (2007), the finance literature has established that "[s]ingle factor models such as the Capital Asset Pricing Model (CAPM) do not capture all of the types of systematic risk that influence firm cost of capital. In particular, the CAPM does not reflect the empirical evidence that supports both a size-related and a book-to-market related systematic risk factor."

[26] As estimated by Vernon in comments filed with the FTC during its comment period. This is consistent with Myers and Shyum-Sunder, 1996 (Myers, S., and Shyum-Sunder, L., "Measuring Pharmaceutical industry risk and the cost-of-capital," In: RB Helms, editor, *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, AEI Press (1996), pp. 208-237), who estimate a 14% real cost of capital for seven medium-sized publicly traded biotech and pharmaceutical firms for 1989. Brill cites this paper, but neglects to mention the 14% estimate in the paper or their corresponding analysis of "small" firms (including Biogen, Cetus and Genentech, along with other firms like Scherer and Mylan, with lower average betas than the true biotechs); the small firm sample had real equity costs of capital of 16.1% (p. 228), and higher if one just used biotech firms.

- Grossman (2003) estimates the cost of capital for smaller biotechnology firms and finds that biotechnology firms without a marketed product but with one or more biologic candidates in Phase II or III trials have an average nominal cost of capital of 27.4%.[27] He also estimates a nominal cost of capital for biotechnology firms with at least one biologic approved of 18.17%.[28] Again assuming a 3% annual inflation rate, these figures would correspond to real costs of capital of 23.69% and 15.24%, respectively.

Consistent with these findings, many small biotechnology firms rely heavily on venture capital for financing, which typically implies very high cost of capital requirements, and biotechnology firms are facing increasing difficulties obtaining this financing in the face of the current credit crunch.[29] Table 1 summarizes biotechnology industry cost of capital figures from a wide range of sources.

Brill relies on a real cost of capital of 10%, which is far lower than estimates typically reported in the academic or trade literature for the biotechnology industry. His results are also highly sensitive to increases in this estimate.[30] Brill claims to substantiate his 10% cost of

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[27] Grossmann, M., *Entrepreneurship in Biotechnology*, Physica-Verlag New York, 2003.

[28] Myers and Howe (1997) similarly find that smaller biotech firms had much higher betas (measures of risk) than larger biotech companies, which would result in substantially higher cost of capital for smaller firms. They estimate an average beta in 1992 of 1.38 for "mature" biotech firms, 2.38 for biotech firms with drug candidates in advanced stages of clinical testing, and 2.17 for biotech firms without drug candidates in advanced stages of clinical testing.

[29] See for example, Boyle, C., "Credit Crunch Threatens Investment in Medicines," TimesOnline, October 27, 2008.

[30] Brill's claim in footnote 9 of his paper that breakeven still occurs with a cost of capital of 11.5% and a 7 year data exclusivity period is not accurate (even if one relies on his assumed 60% profit margin). Prior to correcting for errors in Brill's calculations, his model yields a 17 year breakeven period with a cost of capital of 11.5% rather than 10%; after correcting the calculations in his model but keeping all inputs other than cost of capital unchanged there is no breakeven in the first 50 years.

capital assumptions by citing the paper, DiMasi and Grabowski (2007), along with Myers and Shyam-Sunder (1995), and by citing a website maintained by Damodaran:

- Brill's interpretation of DiMasi and Grabowski,(2007) as being consistent with a 10% cost of capital is not correct. The 10% estimate is the lowest of several estimates found (other estimates included 12 and 12.5%) and reflects a period of low risk-free rates and risk premiums. Investors will consider *long-term* investment conditions, however, and the lower observed short-term period of risk-free rates and risk premiums are unlikely to be a reliable guide as to long-term future rates and premiums. Furthermore, the estimate is based on relatively large, publicly traded biotech and pharmaceutical companies and does not reflect the cost of capital of small or mid-sized biotechs.
- In discussing DiMasi and Grabowski (2007), Brill also cites Myers and Shyam-Sunder (1995), but ignores their 1989 analysis of "small" firms that finds a real equity cost of capital of 16.1%, or even higher if one examines just biotech firms. Their "small" firm sample actually includes several well-established companies that are now leaders in the biotech field.[31]
- Using data on a website maintained by Damodaran, Kotlikoff (2008) finds the real cost of capital as of January 2008 to be 12.7% for biologic firms. To calculate this cost of capital he uses a risk-free rate based on U.S. Treasury inflation protected securities ("TIPS") of 2%. Brill relies on the same data but estimates a real cost of capital of 10.25%, apparently suggesting that Kotlikoff's estimates are overstated. To arrive at a lower cost of capital than Kotlikoff, it is likely the case that Brill is assuming a lower

[31] Such as Biogen and Genentech, along with other firms like Scherer and Mylan with lower average betas than the true biotechnology firms.

risk-free rate and a lower equity premium. In fact, Brill's risk-free rate would need to approach zero to account for the difference between his and Kotlikoff's cost of capital estimates, as the other input data currently available from Damodaran's website appear to be unchanged from those relied on by Kotlikoff.[32] Biotech firms and early stage investors cannot and do not change their R&D investment decisions based on monthly changes in U.S. Treasury rates, however, as would be suggested by Brill's analysis of the Damodaran data. In comparison, the 13.25% real cost of capital estimate found by Golec and Vernon (2007) reflects a superior approach that is longer-term in focus and less susceptible to such volatility.

Relying on cost of capital inputs that do not accurately reflect the actual biotech industry cost of capital to determine an exclusivity period risks adverse effects on financing. This would severely restrict investment in the development of new therapies and have a potentially strong negative effect on competition. As discussed earlier, the costs of capital for firms without marketed products exceed the industry average substantially and would be particularly adversely affected.

[32] The sample of companies that Damodaran relies on for the biotechnology industry includes a number of firms that are not true biotechs for the purposes of this paper, including: Luminex, a bioassay testing firm; Martex Biosciences, which markets supplements; Ista, primarily focused on small molecule opthamalic products; and Mamatech, which develops breast tumor detection products.

VI. CONTRIBUTION MARGINS OF 60 PERCENT ARE TOO HIGH AND REFLECT THE EXPERIENCE OF ONLY A FEW OF THE LARGEST AND MOST SUCCESSFUL FIRMS

The *Nature* article simulations rely on a 50% contribution margin,[33] which is based on the contribution margins realized by the eight largest biotech firms with multiple products on the market. However, few biotech companies are actually profitable, and the universe of biotech firms is populated with development-stage companies whose principal assets are their human capital and intellectual property. These companies would be expected to experience lower contribution margins than a firm with an established line of approved products as represented by the sample that reflects even a 50% margin.

Brill argues for a much higher contribution margin of 60%, which is not reflective of the expected profit potential for most biotechnology products. He bases this estimate on a market-capitalization-weighted average of large and very successful companies, which has the effect of biasing his figure upward and is not representative of the sector.

Brill's use of market-capitalization weighting means that his average margin primarily reflects just two biotech firms with large market capitalizations relative to the other firms in his sample. Even among Brill's six highly successful companies, many of them earn margins well below his 60% average, and there is considerable variation in margins from 43.4% to 63.7%.

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[33] As noted earlier, the contribution margin is a measure of how much a company earns in sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative (SG&A) expenses. It is expressed as a ratio of sales, less cost of goods sold and less SG&A, to sales. Contribution margin is not equivalent to profit margin, which also subtracts the costs of R&D, and interest, taxes and all other expense items. All calculations of the contribution margin in this paper were based on publicly available sources.

Furthermore, three of the six firms identified by Brill earn margins of 50% or less over the 2001 to 2007 time period that he examines.

Two of the largest biotechnology not identified in Brill's sample that qualify for inclusion and were independent firms during the time period examined earned average margins of 36% and 35%, respectively, during the 2001 to 2007 period, substantially lower than Brill's 60% margin assumption.[34] Including these two additional firms, the range in margins over the time period would be 33.6% to 63.7% with five of the eight biotechnology firms reviewed earning margins of 50% or less.

Not only do a number of highly successful biotech companies fail to earn contributions margins consistent with his 60% assumption, but contribution margins for medium and smaller biotechnology companies would also be far lower than 60%.

Relying on Brill's overly optimistic contribution margin assumption to determine appropriate exclusivity periods for biologics would result in estimated breakeven periods that are too low. If these figures are used to determine data exclusivity period limits, it would have the effect of making investment in some potentially important innovative biotech products too unattractive to warrant the cost and risk of investment..

VII. BRILL HAS IGNORED OTHER COUNTERVAILING ASSUMPTIONS IN THE PRIOR *NATURE* ANALYSIS

The *Nature* analysis imposes a number of countervailing assumptions that are likely to overstate expected revenues and understate expected costs, resulting in breakeven periods that err on the side of being shorter than what would actually be experienced in the biotechnology

[34] These firms are MedImmune and Chiron.

industry. Brill fails to note any of these countervailing assumptions in his critique, or the fact that reasonable alternative assumptions result in longer breakeven periods, and potentially no breakeven point using his cost of capital, contribution margin, and seven-year data exclusivity assumptions. These countervailing assumptions include:

(1) ***The lowest quintile of sales is excluded when estimating the expected average revenue stream.*** Excluding the lowest quintile results in estimates that potentially overstate expected revenues, and understate expected breakeven periods.

(2) ***A very low rate of product obsolescence from new biologics is assumed.*** Specifically, the *Nature* model assumes no product obsolescence in the first 10 years following release, and only a 3.5% annual reduction in sales after 10 years. The recent surge in the biologic product pipeline and R&D growth for biologics suggests that a faster rate of new product introduction, and therefore a higher rate of obsolescence (shorter product life cycles) may apply than that assumed in the *Nature* model. Currently, over 600 biologics are in development.[35] This low rate of product obsolescence further serves to potentially overstate the expected revenue stream from successful biologics. Including the effect of more robust brand-to-brand competition would produce longer required breakeven periods.

(3) ***Finally, the Nature model assumes that firms are able to utilize existing plants with no retrofitting costs.*** The *Nature* model assumes that product validation costs are the only costs required to produce successful biologic products. In actuality, many firms may face

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[35] The Pharmaceutical research and Manufacturers of America (PhRMA). Medicines in Development – Biotechnology 2008. PhRMA web site (online), http://www.phrma.org/images/110308%20biotech%202008.pdf (2008).

substantial upfront capital investment costs. The model may therefore understate expected costs of bringing a biologic product to market and, thus, understate expected breakeven periods.[36]

VIII. SOME FURTHER EXTENSIONS AND SENSITIVITY ANALYSIS OF THE *NATURE* MODEL

Data exclusivity periods should be established that are robust to alternative reasonable assumptions for contribution margin, cost of capital, biosimilar share, and brand price discounts in response to biosimilar entry. Brill relies on the following assumptions:

- Contribution margin of 60%
- Biotech cost of capital of 10%
- Biosimilar shares increasing from 10% in the first year to 35% by the fourth year of biosimilar entry
- Brand price discounts increasing from 20% in the first year to 40% by the fourth year of biosimilar entry.

This section presents the results of sensitivity analyses on a range of potential values for each of these key assumptions.

A. SENSITIVITY ANALYSES ON COST OF CAPITAL AND MARGIN ASSUMPTIONS

Table 2 presents the results of sensitivity analyses on breakeven period findings for different cost of capital and contribution margins, and also includes Brill's cost of capital and

[36] Alternatively, this approach is akin to assuming production is outsourced with a contract manufacturing charge equal to book depreciation charges. This also would be a conservative assumption since contractors would have to obtain a margin above depreciation costs to be a viable business.

data exclusivity assumption for comparison. The breakeven periods are reported for data exclusivity periods of 7 years, 10 years, 12 years, 14 years, and 16 years. The results reflect the same biosimilar share and brand price erosion assumptions that Brill uses (i.e., a biosimilar share of 10% in the first year of biosimilar entry, increasing to 35% by year 4, and a 20% brand price discount in the first year of biosimilar entry increasing to 40% by year 4, reflecting a branded competition model). Results indicate that a data exclusivity period of 12 to 16 years is required for breakeven periods of less than 50 years, under reasonable assumptions.

The cost of capital and margin assumptions applied in the sensitivity analyses include:

- The best current estimate now available of the cost of capital for the biotechnology industry is 13.25%, as supported by Golec and Vernon (2007). Breakeven periods are estimated under cost of capital assumptions including the 11.5% and 12.5% assumptions from the *Nature* article, Golec and Vernon's finding of 13.25%, and a real cost of capital estimate of 14.1% based on Ibbotson's median three-factor Fama-French measure. As stated, the 11.5% and 12.5% assumptions are lower than the best current estimates for cost of capital in the biotechnology industry, and therefore would have the effect of understating breakeven periods.
- A contribution margin of 50% is reasonable based on large successful biotechnology companies. Half of the companies in the sample of very successful biotechnology companies used by Brill earn contribution margins of 50% or less. Furthermore, small biotechnology companies typically have margins that are substantially lower. As a result, 50% likely overstates the margin that would be earned by an average biotechnology company. The sensitivity of findings is tested by applying average contribution margins of 60%, 55%, 50%, 45%, and 40%.

The cost of capital and contribution margin sensitivities are reported relying on the same biosimilar share and brand price erosion assumptions that Brill implements (his interpretation of the CBO's assumptions in its cost estimate of S. 1695). In addition, sensitivities with respect to alternative biosimilar share and brand price discount assumptions are also calculated in the next section.

In general, results confirm the importance of a substantial data exclusivity period to R&D returns. Notably, with an exclusivity period of 7 years, the *only* combination of assumptions that yields a breakeven point of less than 50 years is the one used by Brill (i.e., a cost of capital of 10% and a contribution margin of 50% or lower). Even with a 12-year exclusivity period, reasonable breakeven periods are possible only under the more extreme assumptions (e.g., if the best current estimate of the cost of capital of 13.25% is assumed, breakeven is achieved only when the contribution margin assumption is 60%, and breakeven is achieved at 17 years).

Exhibits 4(a), 4(b) and 4(c) present the results for cumulative net present value over time for selected data exclusivity periods, assuming costs of capital of 11.5%, 12.5% and 13.25%, respectively, and a 50% average contribution margin. Exhibit 4(a) shows that the cumulative net present value of returns to the innovator approaches a value just above zero when a cost of capital of 11.5% is assumed and a 12-year exclusivity period is applied. The innovator fails to break even if a cost of capital of 12.5% is assumed under either a 12-or 14-year data exclusivity period (Exhibit 4(b)), and if a 13.25% cost of capital is assumed, the innovator does not break even with a 12-, 14-or even a 16-year data exclusivity period (Exhibit 4(c)).

Exhibits 5(a), 5(b) and 5(c) present the same sensitivities as in Exhibit 4 but assume a 55% average contribution margin. With the higher assumed contribution margin, the innovator would be able to break even with a 12 year data exclusivity period but only if the cost of capital

is 11.5% or 12.5% (Exhibits 5(a) and (b)). In this regard, breakeven is achieved for the combination of a 12.5% cost of capital and 12 year data exclusivity period in approximately 17 years (Exhibit 5(b)). Assuming instead the preferred Golec Vernon-derived 13.25% cost of capital, the innovator breaks even only with a 16-year data exclusivity period, but fails to do so with shorter exclusivity periods of 12 and 14 years (Exhibit 5(c)).

B. SENSITIVITY ANALYSES TO ALTERNATIVE BIOSIMILAR SHARE AND BRAND PRICE EROSION ASSUMPTIONS

1. Biosimilar Share and Brand Price Erosion Assumptions

In this section, we report alternative assumptions on biosimilar share and brand price erosion reported in the literature. We calculate the impact of some alternative assumptions on breakeven results in a series of sensitivity analyses.[37] Before presenting these calculations, as background, it is useful to review the CBO report assumptions, together with other studies that have considered the competitive effects of biosimilar entry.

Table 3 shows the peak market penetration and biosimilar price discount estimates from four recent studies. Each of these studies is focused on established biologic products that could experience biosimilar competition over the next several years. Most studies generally acknowledge that biosimilar penetration rates are expected to increase as markets evolve from a regulatory, scientific, and reimbursement perspective. Hence, these estimates tend to underestimate penetration rates for the products which are now in discovery and development. Peak biosimilar penetration rates reflected in various recent studies range from 35 to 60%, with

[37] All of the assumptions in the sensitivity analyses are guided by the existing literature, economic theory, and the judgements of the authors.

the CBO estimate being the most moderate. Some of these figures reflect biosimilar penetration rates only among the largest selling products, however, while the CBO estimate is described as a sales-weighted average. All of the studies are based on comparators that may be imperfect predictors of the future biosimilar market.

Table 3 also displays the corresponding assumptions on biosimilar price discounts relative to the pre-biosimilar entry price of branded products. In this case, the CBO estimate is generally consistent with other sources at least in terms of initial year price discounts. All of the studies shown expect discount rates to reach at least 25 percent over time, especially for larger-selling products where more entrants are expected.

In terms of the branded products' competitive response to biosimilar entry, only one of the sources in Table 3, Avalere, provides an initial estimate of expected branded product's price impacts. [38] In general the Avalere study predicts that the reference brand will decrease prices in response to biosimilar entry.[39] Economic theory suggests that a competitive price response on the part of the innovator is expected, where there is a small number of entrants in these markets.[40]

Given these considerations and possibilities, further sensitivity analyses appear warranted on biosimilar share and the brand's price response.

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[38] Ahlstrom, A., et al., "Modeling Federal Cost Savings from Follow-On Biologics, White Paper, Avalere Health, April, 2007 < http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf >, accessed December 20, 2008.

[39] Avalere has indicated they are refining their estimates on branded share and price impacts as new information becomes available.

[40] Grabowski, H., Ridley, D., and Schulman, K., "Entry and Competition in Generic Biologics," *Managerial and Decision Economics*, 2007, 28(4-5), pp. 439-451.

2. Results of Sensitivity Analyses

Table 4 presents the breakeven period findings for alternative assumptions on biosimilar share and brand price erosion. Specifically, we test the following brand share and price erosion assumptions:

- ***Biosimilar share*** is assumed to be 10% in the first year of entry regardless of scenario, but we test alternative steady-state biosimilar shares in year 4 of 25%, 35%, 45%, and 55%. The 35% assumption is consistent with Brill's assumptions; other values are associated with other recent estimates shown in Table 3.
- ***Brand price erosion*** is assumed under three scenarios: to be 0% in all years (i.e., no increase or decrease in real brand prices from the point of biosimilar entry); to be a 10% brand price decrease in year 1, increasing to a steady-state decrease of 25% by year 4; or to be a 20% decrease in year 1, increasing to a steady-state decrease of 40% in year 4, relative to real prices at the point of biosimilar entry.[41] The scenario that assumes brand price erosion increasing from 20% to 40% in the first four years is consistent with Brill's assumptions.

As shown in Table 4, a 10 year data exclusivity period is consistent with breakeven only in the extreme case where both the cost of capital and margin assumptions fall beyond the best baseline estimates.

All of the above described sensitivity analyses reflect a cost of capital of 13.25% and a contribution margin of 50%. The breakeven periods are reported for data exclusivity periods of

[41] Since over time nominal prices for biologics are expected to be adjusted for inflation and other factors, reductions have been reflected on a real, or inflation-adjusted, basis in the *Nature* model. Assuming no real price changes implies nominal price will increase only with inflation.

7 years, 10 years, 12 years, 14 years, and 16 years. As in the earlier sensitivity analyses, the results for these brand share and price erosion sensitivity analyses suggest that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period of time, under reasonable assumptions.

As a further sensitivity analysis, Table 5 presents results for similar calculations as those presented in Table 4, but assuming a lower cost of capital of 12.5% and a higher contribution margin of 55%. The results in Table 5 are likely to understate breakeven periods as the cost of capital is lower than the best estimate for biotechnology investments and the contribution margin is higher than for many biotechnology companies. Nevertheless, data exclusivity periods of less than 12 to 16 years are still associated with long, or no, breakeven period. For data exclusivity periods of 7 years, breakeven periods of less than 50 years only occur with no brand price discounts and limited biosimilar shares. For data exclusivity periods of 10 years, breakeven periods of less than 20 years only occur with no brand price discounts; and breakeven periods of less than 50 years occur with moderate brand price discounts (10% to 25%) and limited biosimilar shares.

The analysis presented by Brill and the sensitivity analyses that are presented in this paper are based on worldwide revenues, and it should be noted that these worldwide revenues will be affected by variation in data or market exclusivity periods worldwide. In a review of top selling biologic drugs, the U.S. market is by far the most significant, varying substantially depending on where the drug is in its life cycle.[42] As a result, because volume is a key driver,

[42] According to a December 12, 2008 telephone call with a Sanford C. Bernstein & Co. analyst, in 2008, U.S. sales as a percentage of world-wide sales for all tracked biologic products are expected to average

U.S. data exclusivity periods are likely to have the most significant impact on biologic revenues and investor decisions.

IX. SUMMARY AND CONCLUSIONS

Identifying an appropriate data exclusivity period for biologics is an important component of any bill meant to establish an abbreviated regulatory pathway for biosimilar entry. The data exclusivity period is an essential component in allowing investors to earn a market return on biotechnology investments. As a result, continued investment in biotechnology research, and the valuable new products that such investment will produce, is dependent upon the establishment of an appropriate data exclusivity period in conjunction with any legislation establishing an abbreviated biosimilar regulatory approval pathway.

Appropriately modifying the Nature article breakeven model to consider the effects of biosimilar entry on market shares and prices indicates that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period, under reasonable assumptions. An adequate exclusivity period is necessary to maintain incentives to invest in the development of innovative new biologic products.

This finding is in stark contrast to the seven-year data exclusivity period suggested by Brill and others, and reflects the correction of errors in Brill's application of the model and the sensitivity of Brill's results to small changes in the key assumptions.

66%. Danzon and Furukawa (2006) previously report that U.S. biologics spending represented 63% of the ten countries examined in 2005.

As discussed in the earlier *Nature* article, analyses of breakeven lifetimes, based on historical cost and revenue data, are only one guidepost for selecting appropriate data exclusivity periods. The future environment for biologic innovation may differ from the past in many important ways – including the cost of development, prices and sales revenue, and the intensity of competition from branded therapeutic alternatives and from biosimilars. Nevertheless, a substantial data exclusivity period also appears to be consistent with a few core principles and facts that were outlined in that article and the introduction to this paper:

- Biologic introductions have been among the most novel therapies directed at life threatening and disabling diseases and offer hope for many important unmet medical needs for thousands of patients.
- There is currently a rich pipeline of product candidates in discovery and development from a spectrum of small start-up firms to larger established entities. Most of this pipeline emanates from firms without marketed products whose investors are very sensitive to expected future returns and risks, as many product candidates never make it to market, and there is no guarantee that those that do will be successful. Even for larger firms, the risk and investment associated with biologics research and development is large.
- The nature of patent protection for biologic products necessitates a strong complementary data exclusivity form of protection.

Given the tremendous potential benefits to patient from new biologics, setting a sufficient data exclusivity period to maintain investment incentives under a range of reasonable assumptions about expected returns should be an important consideration.

Appendix – A Note on Brill's Computational Inconsistencies

The sales and price erosion assumptions that Brill relies upon require three modifications to the model presented in the *Nature* article based on the time of biosimilar entry:

(1) Brand biologic revenues must be reduced based on the assumed brand price discount in response to biosimilar entry, and according to the time path of assumed price discounting. This adjustment reflects the fact that even if the same number of units of the brand product are sold, those sales generate less revenue due to the price discount.

(2) The assumed profit margin earned by the brand biologic must be adjusted to reflect the fact that brand price discount results in a smaller margin. Moreover, in computing margins one also expects costs to decline given changes in output and sales. It is reasonable to assume that production and other costs will decline in proportion to output reductions.

(3) Brand biologic revenues must be reduced by the assumed share of sales that the biosimilar is assumed to capture, and according to the time path of assumed biosimilar penetration. This adjustment reflects the fact that fewer units of the brand may be sold following biosimilar entry. Similarly, non-R&D production costs must be adjusted proportionately.

Brill makes the second and third of these modifications, but fails to implement the first. As a result, he overstates the level of brand biologic revenues following biosimilar entry that would be implied by his assumptions.

As an example for purposes of illustration, assume the following set of facts, and perform the associated calculations:

- Assume brand revenues in absence of biosimilar entry are $1,000.
- Further assume that with biosimilar entry, the biosimilar captures 35% of unit sales and the brand reduces its price by 40%.
- Brand revenues for determining cash flow in the presence of biosimilar entry are then $390, calculated as: $1,000 x (1 – 35%) x (1 – 40%) = $390, to which one would then apply the appropriate profit margin. Assuming that after taking account of the price changes, the appropriate margin in this illustrative example of 50% , the total margin contribution would be $195.

Brill's calculation error would instead yield the incorrect figure of $650 in brand revenues, calculated as $1,000 x (1 – 35%), and $325 in total margin contribution, again assuming a 50% margin.[43]

[43] The margin is assumed to not be affected by the share penetration of the biosimilar; that is, the share of unit sales captured by the biosimilar is assumed to reduce costs and revenues proportionally. Conversely, the brand price decline is assumed to reduce revenues but not costs, resulting in a lower margin.

Table 1

Cost of Capital Estimates for the Biotechnology Industry

Source	Sector/Group	Model	Cost of Capital	
			Nominal	Real
Golec & Vernon (2007)	Biotech industry-wide	Fama-French	16.75%	13.25%
Ibbotson [1]	Median	Fama-French	17.49%	14.07%
Grossman (2003) [2]	Large drug companies	CAPM	15.70%	12.33%
	Biotech with ≥1 drug approved	CAPM	18.70%	15.24%
	Biotech drugs in phase II or III trials	CAPM	27.40%	23.69%
	Medium-sized publicly traded	CAPM	19%	14%
Myers and Shyam-Sunder (1995)	Small firms	CAPM		16%
Grabowski (2008) [3]	Biotech industry-wide	CAPM		11.5%-12.5%

Notes:

Highlighted cells indicate calculated estimates of real cost of capital based on reported nominal values and assuming a 3% annual inflation rate.

[1] The reported number is for the WACC; Ibbotson includes 73 firms in SIC 2836.

[2] Grossman (2003) relies on a nominal risk free rate of 6.8% and a risk premium of 8.6%.

[3] Grabowski (2008) estimates are based on DiMasi and Grabowski (2007).

Table 2
Breakeven Periods in Years

Alternative Cost of Capital and Contributions Margin Assumptions
Seven-and Ten-Year Data Exclusivity Periods

7-Year Data Exclusivity Period:

Cost of Capital \ Contribution Margin	60%	55%	50%	45%	40%
10%	13.5	>50	>50	>50	>50
11.5%	>50	>50	>50	>50	>50
12.5%	>50	>50	>50	>50	>50
13.25%	>50	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

10-Year Data Exclusivity Period:

Cost of Capital \ Contribution Margin	60%	55%	50%	45%	40%
11.5%	10.6	14.5	>50	>50	>50
12.5%	17.4	>50	>50	>50	>50
13.25%	>50	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

Sources:

[1] Calculations based on the *Nature* model and Brill's interpretation of CBO assumptions for market share and price decline.

[2] Real costs of capital:

11.5% and 12.5% - Grabowski (2008)

13.25% - Golec and Vernon (2007) and Vernon (2008)

14.1% - Ibbotson median Fama-French WACC for SIC 2836, assuming 3% inflation.

Notes:

[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.

[2] Cells highlighted in pink reflect no breakeven within a 50 year period.

Table 2 (Continued)
Breakeven Periods in Years

Alternative Cost of Capital and Contributions Margin Assumptions
Twelve-, Fourteen-, and Sixteen-Year Data Exclusivity Periods

12-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin 60%	55%	50%	45%	40%
11.5%	10.4	11.4	14.2	>50	>50
12.5%	11.9	17.3	>50	>50	>50
13.25%	17.1	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

14-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin 60%	55%	50%	45%	40%
11.5%	10.4	11.4	12.9	>50	>50
12.5%	11.9	13.5	>50	>50	>50
13.25%	13.6	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

16-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin 60%	55%	50%	45%	40%
11.5%	10.4	11.4	12.9	15.4	>50
12.5%	11.9	13.5	16.3	>50	>50
13.25%	13.6	16.4	>50	>50	>50
14.1%	18.9	>50	>50	>50	>50

Sources:

[1] Calculations based on the *Nature* model and Brill's interpretation of CBO assumptions for market share and price decline.

[2] Real costs of capital:

11.5% and 12.5% - Grabowski (2008)

13.25% - Golec and Vernon (2007) and Vernon (2008)

14.1% - Ibbotson median Fama-French WACC for SIC 2836, assuming 3% inflation.

Notes:

[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.

[2] Cells highlighted in pink reflect no breakeven within a 50 year period.

Table 3

Biosimilar Assumptions
In Several Recent Studies

Source [1]	Peak Biosimilar Penetration Rate	Basis	Biosimilar Price Discount (Relative to Pre-Entry Brand Price)
CBO (2008)	10% (year 1) to 35% (year 4)	Similar market situations	20% (year 1) to 40% (year 4)
Grabowski, et. al. (2007)	10 - 45%	Higher estimates correspond to complex small molecules	10% - 30% (year 1)
Express Scripts (2007)	49%	Therapeutic alternatives	25% (year 1)
Avalere Health (2007) [2]	60%[2]	Average small molecule generic drug penetration rates	20% (year 1) to 51% (year 3)

Notes:

1. Congressional Budget Office, Cost Estimate: S.1695 Biologics Price Competition and Innovation Act of 2007, June 25, 2008.
   Grabowski, H.,Cockburn, I., Long, G. and Mortimer, R. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," Duke University, Department of Economics Working Paper, August, 2007.
   Miller, S., and Houts, J., "Potential Savings of Biogenerics in the United States," whitepaper, Express Scripts, February 2007.
   Ahlstrom, A., et al., "Modeling Federal Cost Savings from Follow-On Biologics," whitepaper, Avalere Health, April, 2007.
2. This estimate is for largest selling products. Avalere Health is conducting further analysis.

Table 4
Breakeven Periods in Years

Sensitivity of Findings to Price and Share Assumptions
13.25% Cost of Capital and 50% Contribution Margin

Biosimilar Share (year 4 and beyond)	Brand Price Discount (Year 1 to Year 4 and beyond)		
	No Price Decline	10% year 1 to 25% year 4+	20% year 1 to 40% year 4+
7-Year Data Exclusivity Period:			
25%	>50	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
10-Year Data Exclusivity Period:			
25%	>50	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
12-Year Data Exclusivity Period:			
25%	>50	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
14-Year Data Exclusivity Period:			
25%	30.3	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
16-Year Data Exclusivity Period:			
25%	25.9	>50	>50
35%	28.7	>50	>50
45%	37.7	>50	>50
55%	>50	>50	>50

Sources:
[1] Calculations based on the *Nature* model.
[2] Real costs of capital 13.25% - Golec and Vernon (2007) and Vernon (2008)

Notes:
[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
[2] Cells highlighted in pink reflect no breakeven within a 50 year period.
[3] Biosimilar share is assumed to be 10% in year 1 for all scenarios.

Table 5
Breakeven Periods in Years

Sensitivity of Findings to Price and Share Assumptions
12.5% Cost of Capital and 55% Contribution Margin

Biosimilar Share (year 4 and beyond)	Brand Price Discount (Year 1 to Year 4 and beyond)		
	No Price Decline	**10% year 1 to 25% year 4+**	**20% year 1 to 40% year 4+**
7-Year Data Exclusivity Period:			
25%	16.9	>50	>50
35%	19.6	>50	>50
45%	27.2	>50	>50
55%	>50	>50	>50
10-Year Data Exclusivity Period:			
25%	14.5	20.7	>50
35%	14.9	24.2	>50
45%	15.5	42.7	>50
55%	16.4	>50	>50
12-Year Data Exclusivity Period:			
25%	13.7	14.4	16.7
35%	13.7	14.5	17.3
45%	13.7	14.5	18.1
55%	13.8	14.6	19.4
14-Year Data Exclusivity Period:			
25%	13.5	13.5	13.5
35%	13.5	13.5	13.5
45%	13.5	13.5	13.5
55%	13.5	13.5	13.5
16-Year Data Exclusivity Period:			
25%	13.5	13.5	13.5
35%	13.5	13.5	13.5
45%	13.5	13.5	13.5
55%	13.5	13.5	13.5

Sources:
[1] Calculations based on the *Nature* model.
[2] Real costs of capital 12.5% - Grabowski (2008)

Notes:
[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
[2] Cells highlighted in pink reflect no breakeven within a 50 year period.
[3] Biosimilar share is assumed to be 10% in year 1 for all scenarios.

Exhibit 1

Cumulative Net Present Value of Cash Flows for Representative Biotech Drug

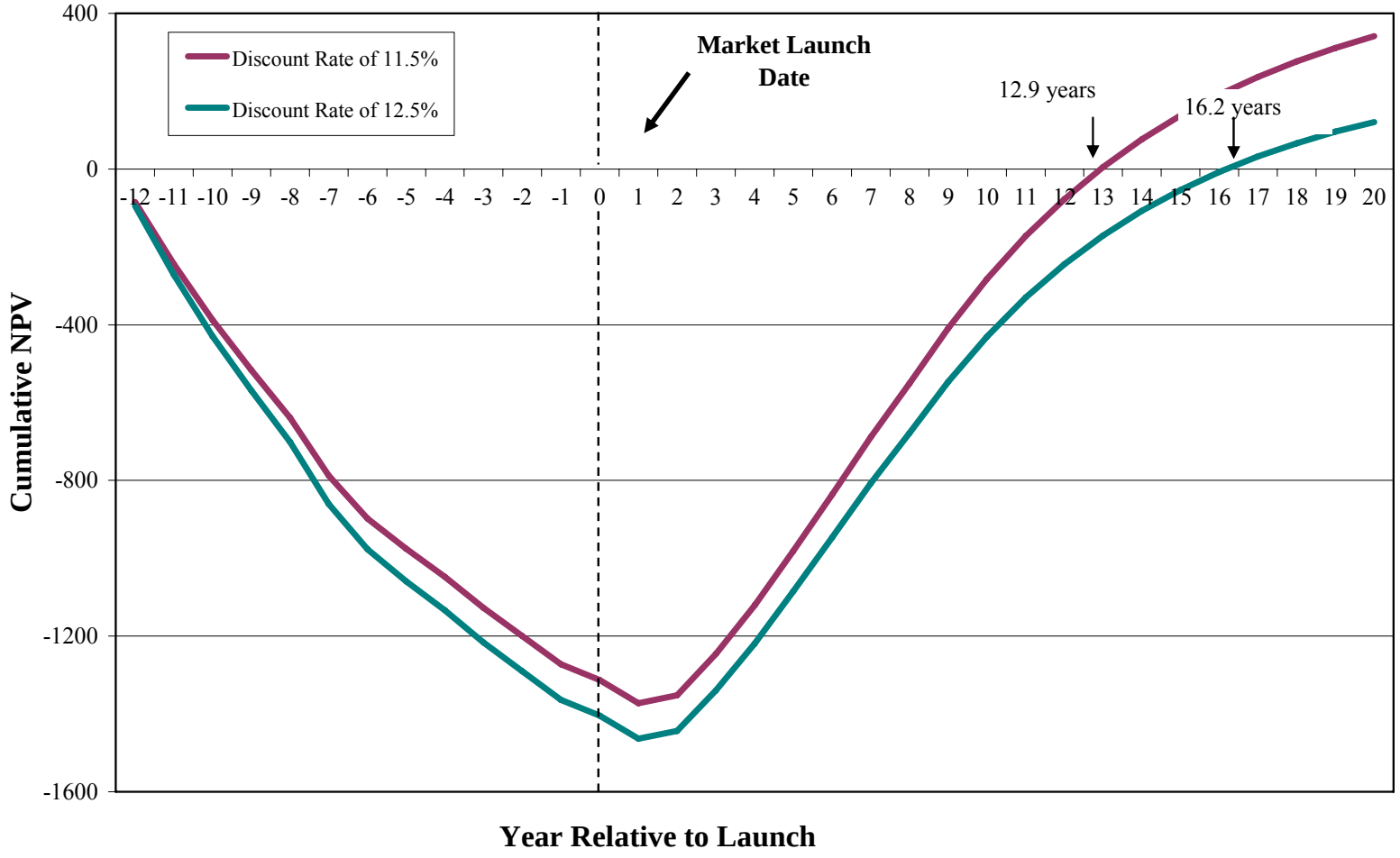
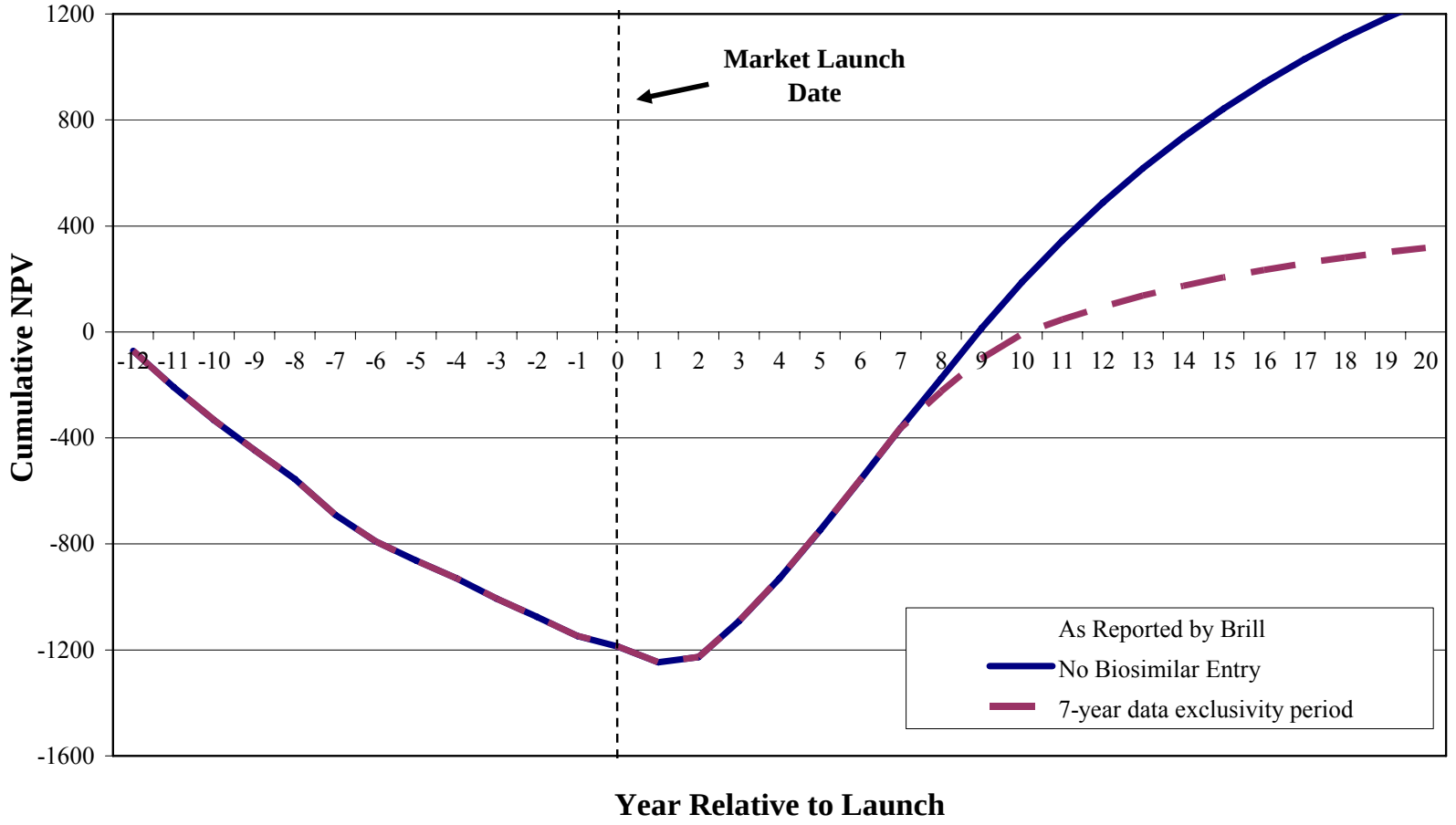


Exhibit 2

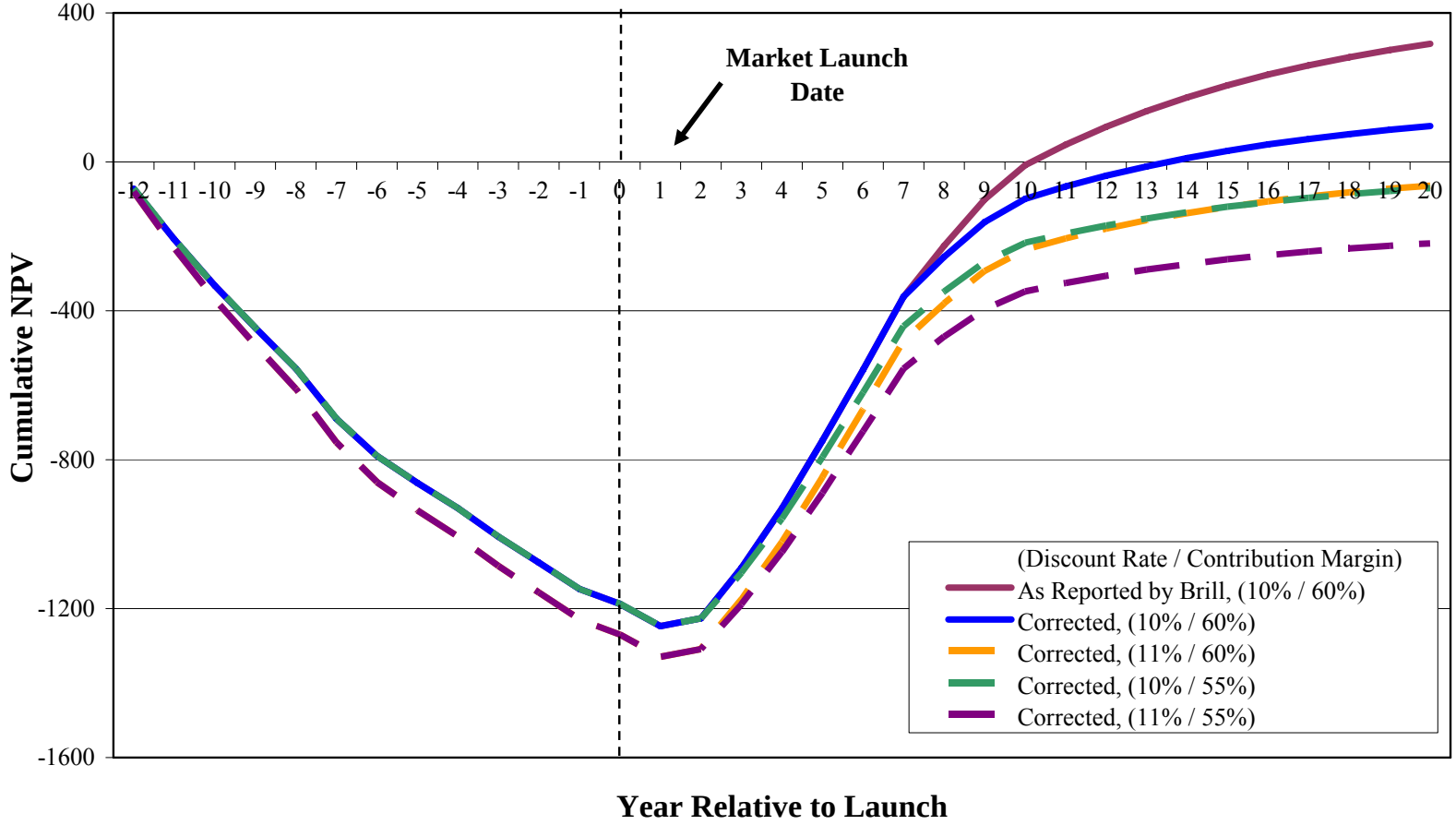
Cumulative Net Present Value of Cash Flows for Representative Biotech Drug
Brill Representation



Note: All scenarios maintain Brill's assumption of a 7-year data exclusivity period and biosimilar share and innovator price discounts, based on his interpretation of CBO share and price assumptions.

Exhibit 3

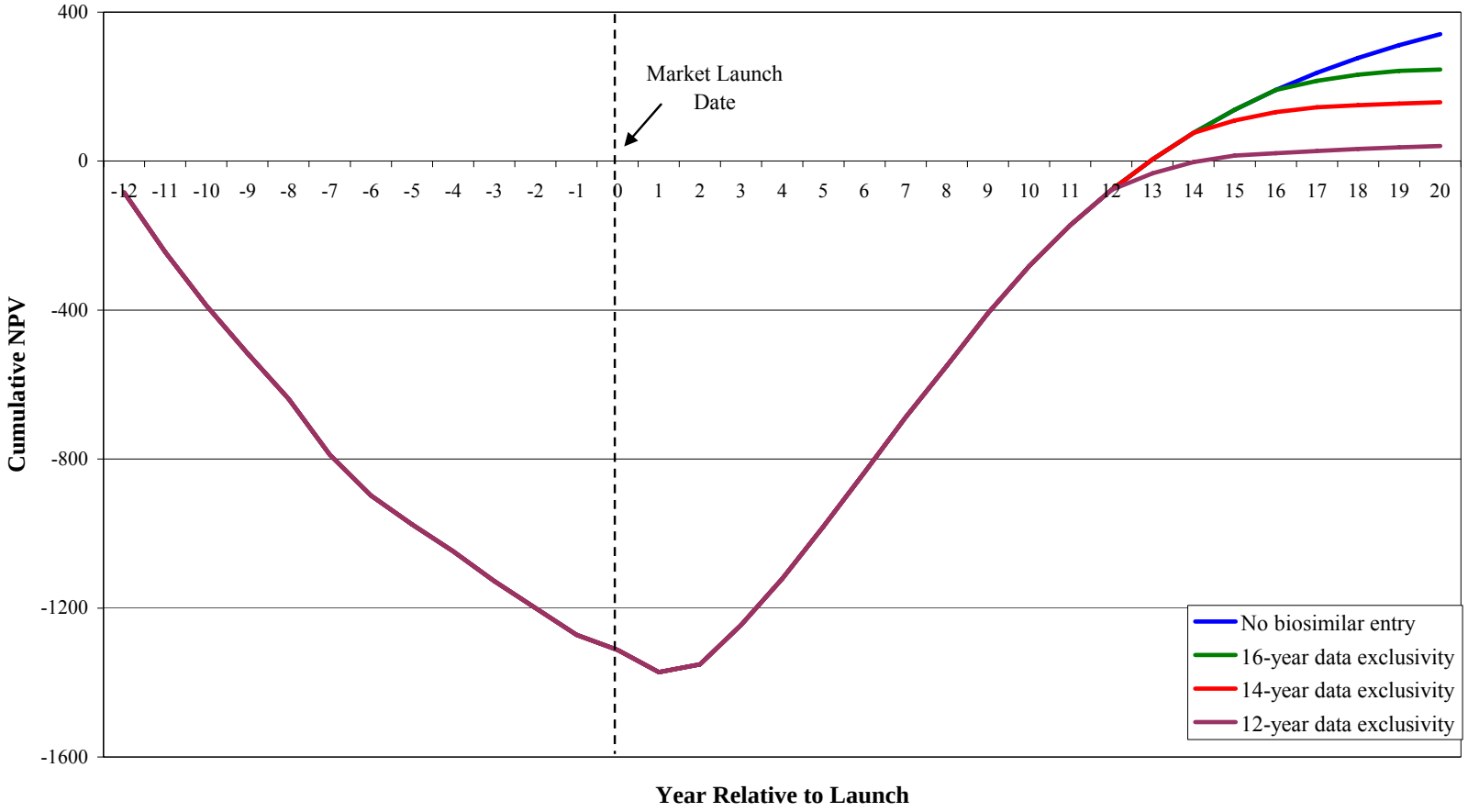
Cumulative Net Present Value of Cash Flows for Representative Biotech Drug
Brill Representation



Note: All scenarios maintain Brill's assumption of a 7-year data exclusivity period and biosimilar share and innovator price discounts, based on his interpretation of CBO share and price assumptions. The innovator does not breakeven within 50 years with either an 11% discount rate, a 55% long-run contribution margin, or both.

Exhibit 4(a)

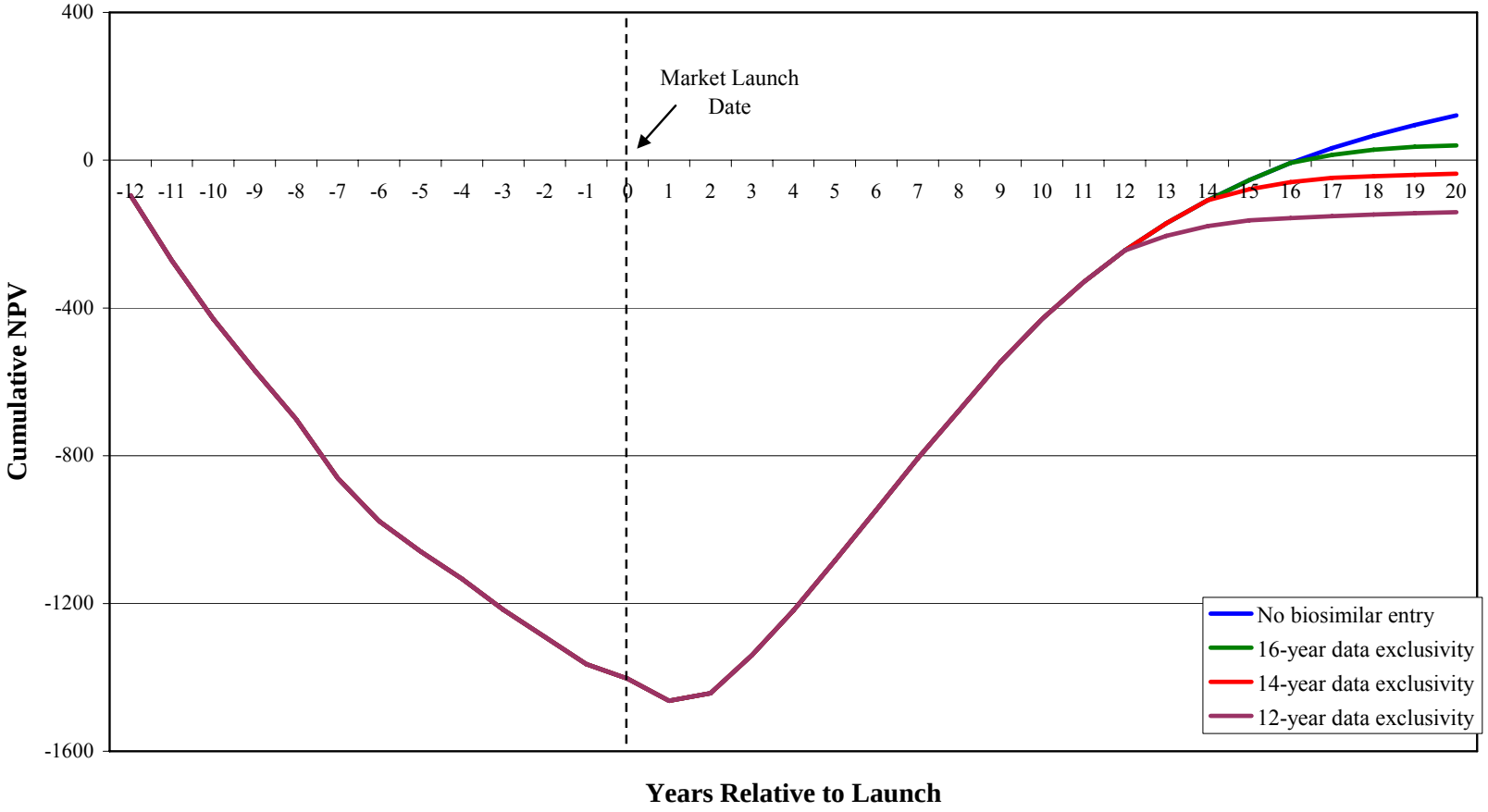
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (50% Average Contribution Margin, 11.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 4(b)

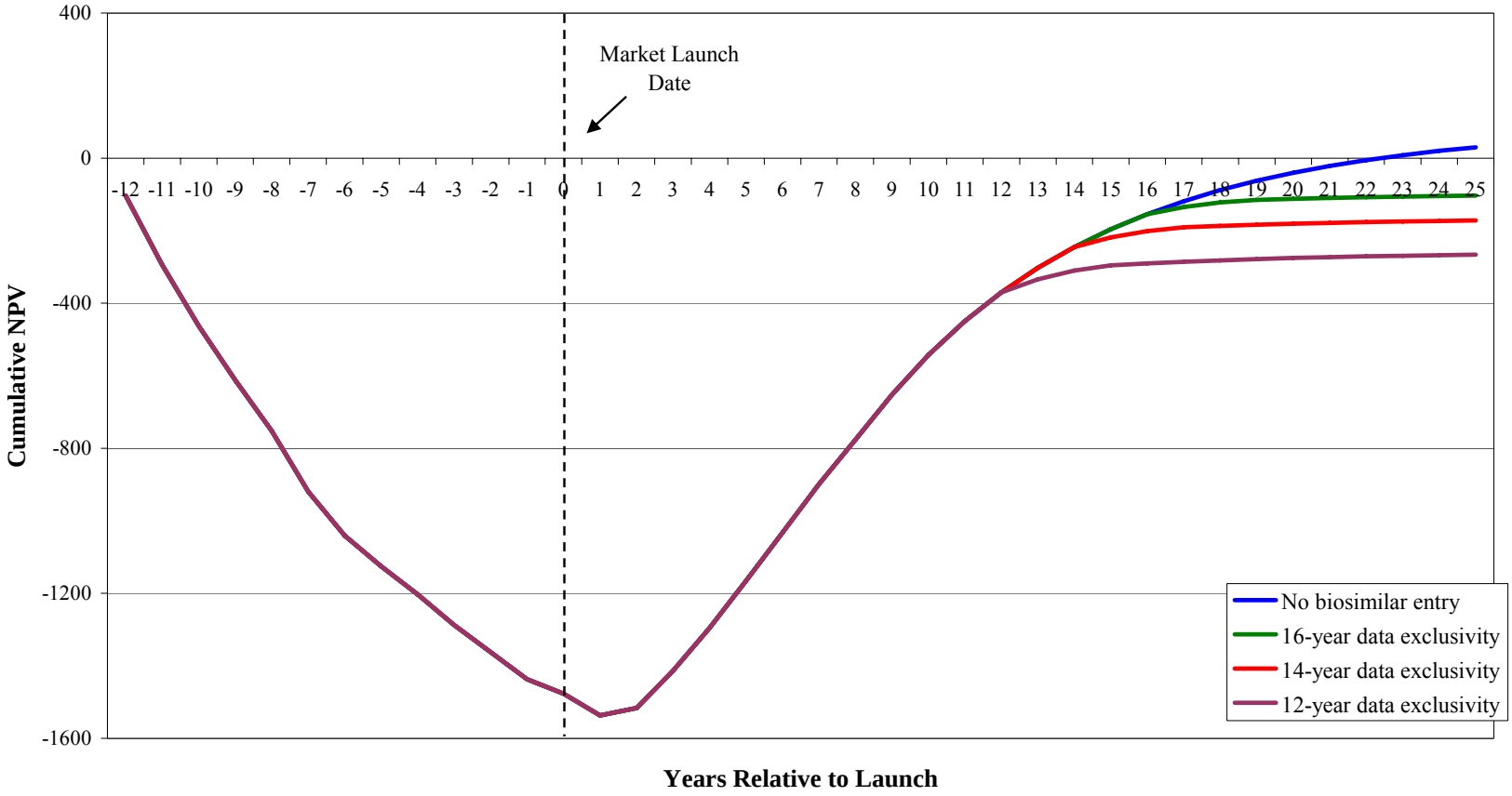
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (50% Average Contribution Margin, 12.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 4(c)

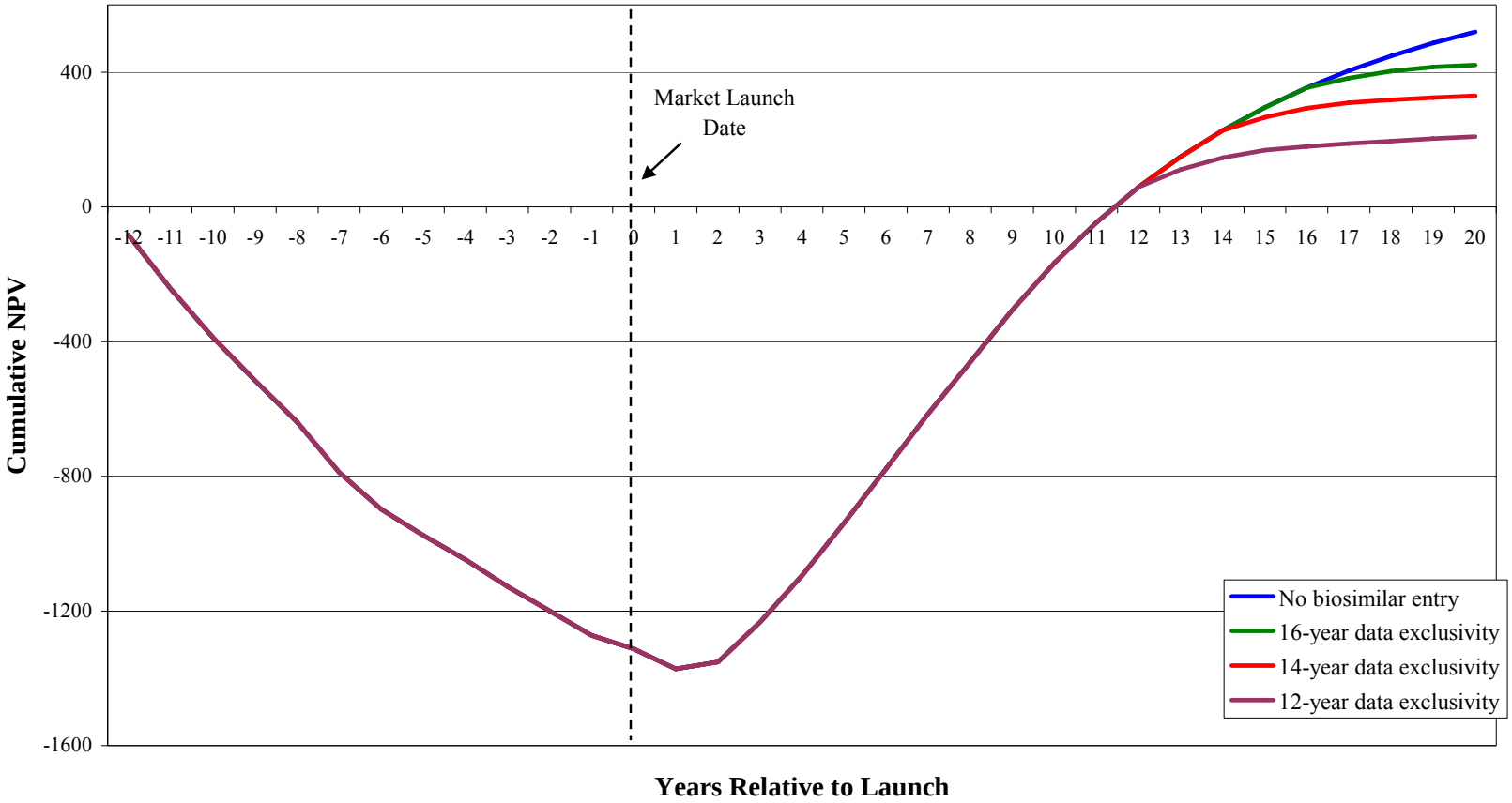
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (50% Average Contribution Margin, 13.25% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(a)

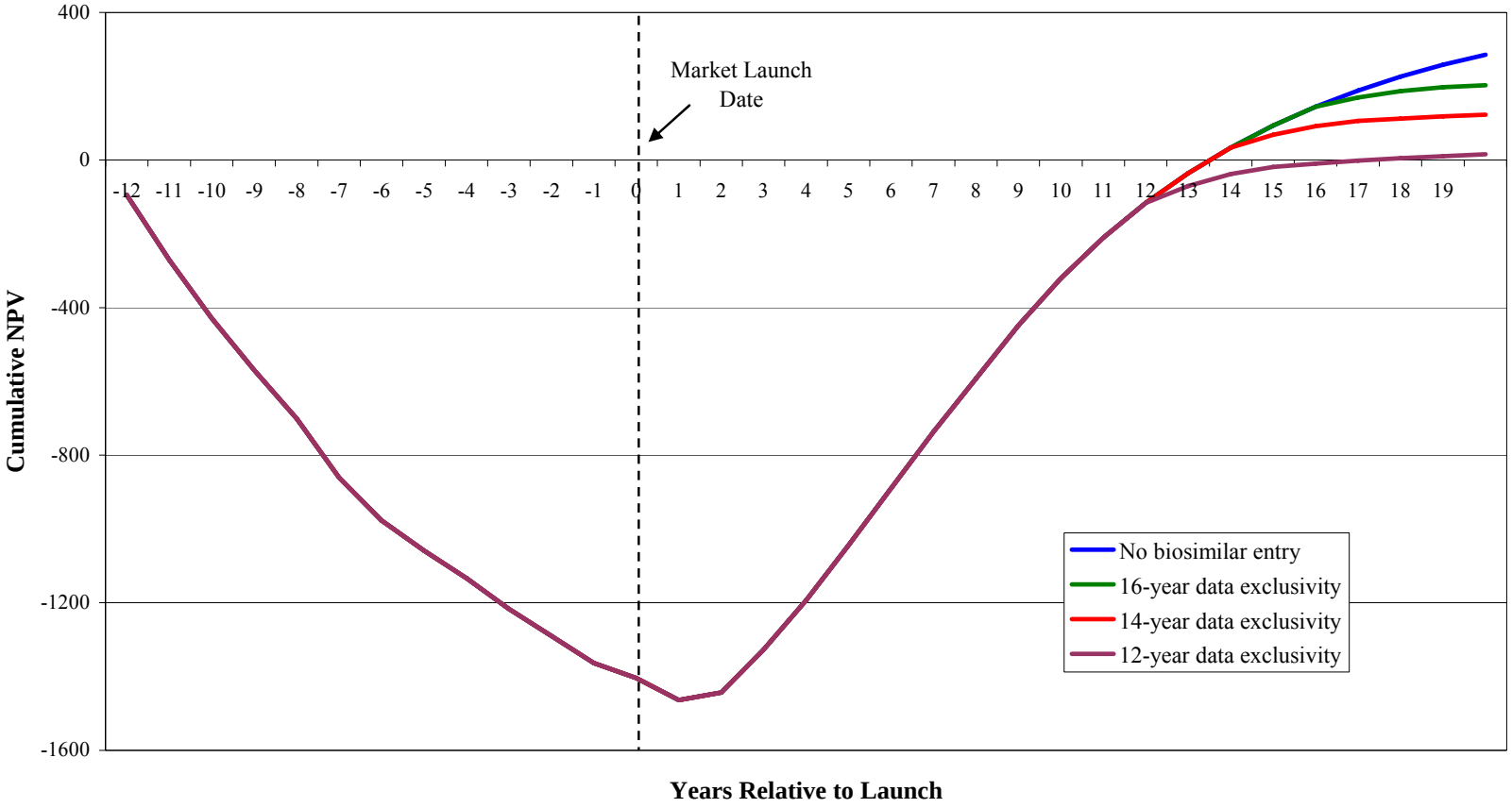
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (55% Average Contribution Margin, 11.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(b)

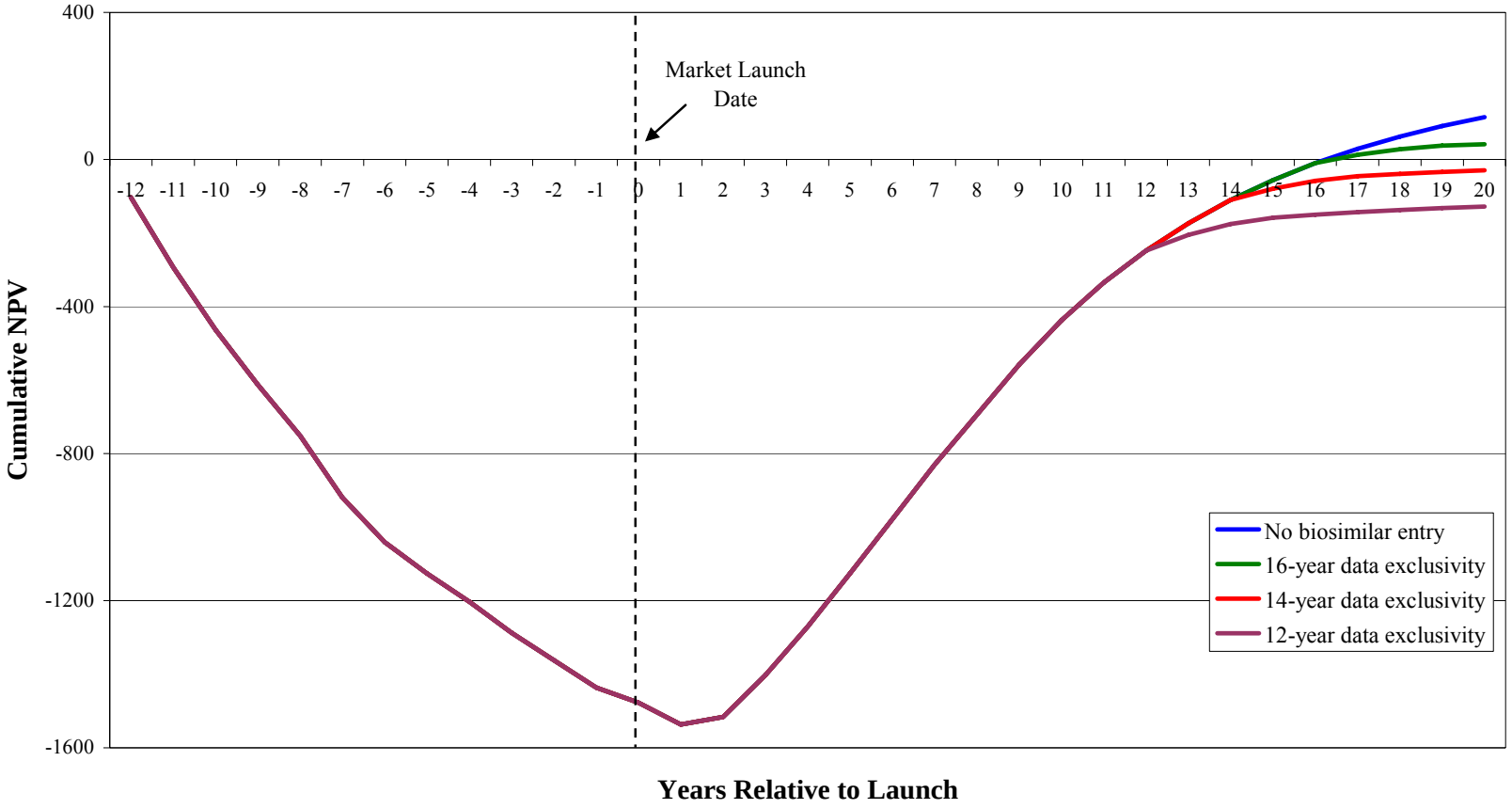
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (55% Average Contribution Margin, 12.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(c)

Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (55% Average Contribution Margin, 13.25% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Attachment D

FTC BIOSIMILARS REPORT REBUTTAL

FTC: Given that biosimilar competition with a pioneer biologic drug is likely to resemble brand-to-brand competition among biologics, the question arises whether provisions that "delay" biosimilar entry and "restrict competition" are necessary to benefit consumers. No economic arguments suggest that such provisions are necessary to foster pioneer drug innovation.

FACT: We agree with the FTC that the market dynamics of biosimilars are more akin to brand-to-brand competition in terms of likely number of entrants, price competition, and market share erosion, at least for the short-term. But this is NOT brand-to-brand competition in one critical respect that the FTC report all but ignores. Brand competitors have to engage in the same lengthy and costly R&D process, from basic invention, through proof of concept, through clinical trials, and full regulatory review and approval, that the initial brand innovator did. Biosimilar manufacturers, on the other hand, will be given a scientific and regulatory short-cut that, while still more demanding than small molecule generic drug entry, will be considerably shorter and cheaper than the process that the initial innovator had to go through. There is a huge difference between the $1.2 billion that is invested on average to produce true innovation, versus the $100-200 million (or less over time) that the FTC suggests a biosimilar manufacturer would have to invest. In no other industry outside of pharmaceuticals do we affirmatively permit (let alone encourage) such "free riding," and to suggest – as the FTC does – that this fact is essentially meaningless in terms of economic incentives for future innovation is baffling. The FTC also phrases its question in a way that is destined to lead to the wrong answer. It is not whether the Congress should enact provisions that delay entry and restrict competition – of course, Congress shouldn't. The proper question is at what point Congress should, when enacting a new pathway designed to facilitate additional competition from biosimilars, allow follow-on manufactures to "free ride" off the work of pioneer companies.

FTC: Nothing about the introduction of biosimilar drug products changes the relationship of pioneer biologic drug products to the patents protecting them. As a result, patent protection should continue to incentivize biotechnology innovation, even after enactment of an approval process for biosimilar drugs.

FACT: In the small molecule, generic drug context, patents do provide the incentives for continued innovation and the period of data exclusivity is less important, because the regulatory approval standard for generics ("sameness") and the patent system (with appropriate term extensions permitted under Hatch-Waxman) work in concert to provide protection against premature generic competition – on average for 12-14 years, as the FTC notes. However, the regulatory approval standard for biosimilars creates a "patent protection gap" that may allow for abbreviated regulatory approval of a biosimilar which does not infringe an innovator's patents. That likelihood exists because of the confluence of two critical factors not present in the Hatch-Waxman construct. First, unlike a generic drug which must be the same as an innovator product, a biosimilar will need only be "similar' to the corresponding innovator product. Indeed, some of the proposed legislation would permit the approval of products that are not very similar to the innovator biologic at all. For example, H.R. 1427, introduced by Energy & Commerce Committee Chairman

Henry Waxman, has a very broad and undefined view of similarity. While the Waxman bill provides for approval of a biosimilar that is highly similar structurally and has the same mechanism of action, dosage form, and strength, it also expressly allows for any or all of these requirements to be waived. Accordingly, the biosimilar product could be quite dissimilar from the innovator's product in structure, in route of administration, mechanism of action, dosage form or strength – or in all of these characteristics – yet still theoretically gain abbreviated approval. This uncertainty will raise substantial questions about the effectiveness of innovator patent protection – a fact that is completely ignored by the FTC report. Second, because of the nature of biologic products – large molecules produced by living cells and organisms through highly specific processes – patent protection is often narrower and easier to "design around" than that of small molecule drugs, and the trend is towards increasingly narrow biotech patents.

FTC: There is little empirical evidence that patent design-arounds have occurred in biologics to any greater degree than with respect to small molecule drugs.

FACT: There is currently no abbreviated biologics approval pathway, and hence much less financial motivation to develop competing "me too" products specifically designed to exploit gaps in the innovator's patent protection. The cost and risk of such an approach in today's market is high, and thus it is unsurprising that there are not many existing cases of biotech patent work-arounds. Yet even without the major incentives of an abbreviated approval pathway, successful biotech design-arounds have occurred (see Hormone Res. Found. v. Genentech, 904 F.2d 1558; Novo Nordisk v. Genentech 77 F.3d 1364; Genentech, Inc. v. Wellcome Foundation Ltd., 29 F.3d 1555; Amgen v. Hoechst Marion Roussel, 314 F.3d 1313; Biogen v. Berlex, 318 F.3d 1132; Genzyme v. TKT, 346 F.3d 1094). These cases illustrate that courts have indeed sometimes taken a very a narrow view of biotechnology patent claims, under which even very 'close' products were determined not to infringe a valid patent. The FTC report focuses on what has happened to date, while ignoring the fundamentally changed incentives once a biosimilar pathway is created.

FTC: Even if the biosimilar manufacturer were to design around the patents claiming a pioneer biologic drug product and enter prior to patent expiration, the pioneer manufacturer will continue to earn significant revenues after biosimilar entry; thus, the effect on the pioneer manufacturer caused by biosimilar entry is not nearly as great as it is with small-molecule generic drug entry and there is no need for data exclusivity to prevent the earlier competitive entry.

FACT: A peer reviewed, published study by Duke University Professor Henry Grabowski looked at this precise question, and found that, even with expected smaller market erosion based on Congressional Budget Office estimates, innovators will not be able to recoup their investment in a reasonable period of time without 12 – 14 years of data exclusivity. While the FTC report offers a critique of this study on other grounds, it never offers any economic data or support for its conclusion that, simply because innovators will still receive substantial revenues after biosimilar entry, there is no need for data exclusivity protections. The FTC report never addresses the fundamental questions raised about the impact of premature biosimilar entry on investment incentives.

FTC: 12-14 years of data exclusivity is too long to promote innovation.

FACT: In fact, the exact opposite is true – 12-14 years of data exclusivity is necessary to continue to foster long-term innovation. The FTC contends that a long period of data exclusivity will hurt innovation. However, currently – with no pathway – there are an unlimited number of years of data exclusivity. Under the current regime, there has been tremendous innovation with the developments of treatments for many diseases such as cancer, rheumatoid arthritis, Crohn's disease to name but a few. The danger of setting the number of years too low is stifling medical advancement and innovation. There is absolutely no evidence that adequate data exclusivity of 12 – 14 years will hamper innovation. In the small molecule world, innovators do not face generic competition for an average of 12-14 years. A similar data exclusivity period for biologics is needed to mitigate against the increased risk created by the similarity standard and patent work-arounds, and achieve parity between small molecule and biotech therapies. Without such parity, there is a real risk that investment incentives will be skewed away from biotechnology – an industry that is largely made up of small companies without profits that are heavily reliant on private investment to fund the R&D process and therefore are particularly susceptible to negative changes in investment incentives.

FTC: Special procedures to resolve patent issues between pioneer and follow-on manufacturers prior to FDA approval are unnecessary and could undermine patent incentives and harm consumers.

FACT: Again, the opposite is true. The early resolution of patent disputes benefits patients, physicians, insurers, follow-on manufacturers and innovators alike. Without a mechanism to resolve patent disputes early – before FDA approval of follow-on products – follow-on products would systematically have to enter the market under a cloud of patent uncertainty. Once on the market, patent disputes over such products would have to play out in high-stakes litigation, causing confusion for patients, physicians, and insurers about the long-term availability of certain products. Congress has recognized that patent disputes over medicines must be resolved as early as possible, and in 1984 created a specific mechanism to litigate patents before generic small molecule drugs are released to the public. The same should be true for biosimilars, so that patients can have the assurance that such products, once released, are there to stay.