Summary of Statement of
Richard Kingham
Before the Subcommittee on Health
of the
House Committee on Energy and Commerce
May 2, 2007

Legislation creating a pathway for approval of similar biological products, or biosimilars, should ensure that those products are safe and effective and maintain adequate incentives for investment in research and development of new biotechnology medicines.

Because of the complexity of their active substances and the likelihood that they will differ from the innovative products to which they refer, biosimilars cannot be treated as generic drugs. Detailed requirements for approval should be developed in public proceedings, taking full advantage of the expertise of innovative manufacturers. Requirements will inevitably include comparative clinical tests, plus special premarketing and postmarketing tests for rare but serious side effects, such as immunogenicity. Biosimilars will not be interchangeable with reference products (or with each other) in the same manner as generic drugs. They should be labeled with distinct names to facilitate postmarketing safety surveillance and detection of rare adverse events.

Any pathway must also maintain incentives for costly and risky investments that are essential to bring new biotechnology-derived medicines to patients, including a substantial period of nonpatent data exclusivity. Legislation should not alter existing rules under patent law that protect innovative products, or make changes that favor biosimilars over innovative products.

The European Union system for regulation of biosimilars, which is summarized in the full statement, provides an instructive example. It includes procedures to ensure that biosimilars are rigorously tested for safety and effectiveness, as well as special measures to detect rare but serious side effects. It also provides a substantial period of data exclusivity, while maintaining key principles of patent law that protect innovative products.

Statement of Richard Kingham

Partner, Covington & Burling

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Subcommittee on Health

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Hearing on

"Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States"

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Mr. Chairman and members of the Committee, thank you for inviting me today. My name is Richard Kingham, and I am a partner assigned to the Washington and London offices of the law firm of Covington & Burling. I regularly represent manufacturers of innovative pharmaceuticals and biotechnology-derived medicines.

Since entering law practice in 1973, I have participated in numerous legislative and regulatory proceedings relating to biological products, including the Swine Flu legislation in 1976, the National Childhood Vaccine Injury Compensation Act in 1986, and recent legislation relating to countermeasures against bioterrorism and pandemic influenza. I took part in the regulatory process relating to several of the first biotechnology-derived medicines in the 1980s and participated in proceedings relating to orphan drug exclusivity for biotechnology products in the late 1980s and early 1990s. I assisted pharmaceutical manufacturers during legislative proceedings leading to enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (the

Hatch-Waxman Act). For the past 17 years, I have acted for pharmaceutical companies and associations in connection with regulatory matters in the European Union, including recent legislative and administrative proceedings relating to similar biological medicinal products, or biosimilars. I have taught pharmaceutical law at the University of Virginia and Georgetown University law schools and at Cardiff University and the University of Wales in the UK, and have served as a member of committees of the Institute of Medicine of the National Academy of Sciences and the National Institutes of Health.

1. Basic Principles for a Regulatory Framework for Biosimilars

As the title for this hearing implicitly recognizes, any legislation creating a pathway for follow-on biological products must be designed to protect patient safety and to preserve incentives for development of new medicines. More specifically, the statutory framework should:

- Ensure that follow-on products are reviewed under the same criteria that apply to innovative products -- based on proof of safety, purity, and potency, as well as adequate manufacturing facilities and controls.
- Recognize that follow-on biologics are not generic drugs. Biologics contain complex active substances manufactured in living systems, so that there will inevitably be differences between follow-ons and reference products that can affect their safety or effectiveness.

- Accept that biological products -- unlike generic drugs -- cannot be approved on the basis of physical and chemical tests of the active substance and bioequivalence studies of the finished product in a small number of healthy subjects. Instead, substantial preclinical testing and clinical studies will be required, including comparative clinical trials to determine whether there are significant differences between follow-ons and reference products in terms of safety and effectiveness. Special attention must be paid to the potential for immunogenicity.
- Provide open, public procedures for all stakeholders to participate in the development of criteria for the approval of follow-on products. Manufacturers of reference products have unique knowledge and experience that should be available to the Food and Drug Administration as it develops requirements for testing follow-on products.
- Acknowledge that, because follow-on biologics will inevitably differ from reference products, it is not possible, in the present state of science and technology, to treat them as interchangeable. This has been clearly recognized by FDA, which stated in a recent submission to the World Health Organization that it "has not determined how interchangeability can be established for complex proteins." If products are deemed interchangeable, patients may be switched from one product to another without the knowledge of the prescribing physician, a situation that would be unacceptable for biosimilars in the current state of science and technology, because they will likely differ from reference products (and from each other) in safety and effectiveness.

- Give FDA clear authority to require measures after approval, including enhanced pharmacovigilance systems, antibody testing, and other studies, to detect rare but serious side effects, such as immunogenicity, that cannot be detected in reasonable programs of pre-market testing.
- Assure that follow-on biologics will be given distinct names, to enable regulators to distinguish them from reference products (and other follow-ons) when evaluating large quantities of data from adverse event reports, which will serve as one of the main mechanisms for detecting differences in the occurrence of rare but serious side effects.
- Include a substantial period of non-patent data exclusivity, during which follow-on applicants may not rely on safety and effectiveness data submitted by the innovator, in order to provide incentives required to bring new biotechnology products to market. The necessary incentives cannot be supplied by patents alone. Data exclusivity and patents serve different purposes. Patents reward inventions, but provide no guarantee that those inventions will be commercialized. For biotechnology products, the initial invention that yields a patent application occurs very early in the research and discovery stage. There follows a lengthy, expensive, and commercially risky period of pre-clinical tests and clinical trials required to determine whether a product derived from that invention will be safe and effective. The whole process typically takes 15 years and entails an investment of $1.2 billion or more, with no guarantee that the end-product will reach the market, or recoup research and development costs if it does. Whatever the strengths or weaknesses of patent protection, society has a

profound interest in creating the incentives necessary for companies to make the investments in research and development required to bring new biotechnology products to patients. A substantial period of data exclusivity is especially important for biotechnology products, because patent protection is often less robust than for small-molecule drugs. Many biotechnology products are protected primarily by process patents or relatively narrowly drawn product patents that may be susceptible to work-arounds, especially under a regulatory regime for biosimilars that permits follow-on products to differ in their structural features from reference products. Ideally, the period of data exclusivity should equal the period of market exclusivity that was contemplated by Congress under the patent term restoration provisions of the Hatch-Waxman Act (14 years), to avoid skewing investment away from biotechnology innovation. I have attached to my testimony a more detailed paper prepared by the Biotechnology Industry Organization, which explains why such a period of data exclusivity is both necessary and justifiable.

- Respect intellectual property and other legal rights. Follow-on biologics legislation should not undermine the patent rights of innovators or diminish protection of trade secrets.

2. The European Experience

The European Union system for approval of similar biological medicinal products, or biosimilars, is broadly consistent with these criteria. It comprises a series of

legislative enactments, guidelines, and policy decisions which, taken together, clearly recognize that the requirements for approval of ordinary generic drugs are not appropriate for biosimilars.

Public proceedings to develop data requirements -- Detailed requirements for data submitted in support of applications for biosimilar products have been developed in public proceedings, leading to general guidance for all biosimilars, more detailed guidance on biotechnology-derived proteins, and guidance for specific product types, such as human insulin, human growth hormone, and erythropoietin. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has established a special working party, composed of experts from the various EU member state governments, to develop these guidance documents. The CHMP typically begins the process by issuing a "concept paper" that identifies the topics it believes should be addressed in a guidance document, and providing interested persons several months to submit detailed comments. Taking account of these comments, the working party then prepares draft guidance documents, which are issued for public comment and circulated to the medicines agencies in all EU member states. This process has ensured that all stakeholders have an opportunity to participate in the development of detailed requirements for follow-ons, and that the EMEA has the benefit of experience that is uniquely available to innovative manufacturers and others outside the Agency. In several cases, draft guidelines have been substantially modified following the public comment period. Public proceedings have, moreover, not significantly delayed the

approval process in Europe. Most guidance proceedings have been completed in approximately a year.

Requirement for clinical testing -- Detailed requirements have been tailored to each product class, but all guidelines issued to date have required comparative clinical trials in addition to physical and chemical assays and pre-clinical tests. Two products have been approved to date, and in both cases substantial comparative clinical trials were required. One application was disapproved, in large measure because data from clinical trials showed that there were significant differences in safety and effectiveness in comparison to the innovative product. It is important to note that these differences would not have been detected prior to marketing but for the requirement to conduct comparative clinical trials.

Special requirements for immunogenicity testing -- The EU has placed special emphasis on measures to detect immunogenicity. This is understandable, because a significant number of patients in the EU suffered from pure red cell aplasia, a rare but very serious side effect caused by a seemingly minor formulation change in one dosage form of an erythropoietin product. In addition to requirements for antibody tests and other measures prior to approval, the EU has required post-marketing tests or enhanced pharmacovigilance activities.

Biosimilars not regarded as generics -- Although the European Medicines Agency does not make therapeutic equivalence determinations (this is instead done

country-by-country, according to varying rules), its guidance on biosimilars states that they should not be regarded as "generics." EU member states that have considered the issue to date have determined that biosimilars should not be substituted for reference products.

Incentives for research and development -- Finally, the EU has ensured that there are substantial incentives for innovative companies to invest in research and development of new biotechnology products. Biosimilar products cannot enter the market until 10-11 years after reference products are approved, and innovators retain all their rights under EU patent laws, including remedies for infringement.

In summary, the European Union has struck a reasonable balance that provides incentives for innovative research and development, provides a clearly delineated pathway for approval of follow-ons after exclusivity periods expire, and ensures that follow-on products will be safe and effective.

3. Applying Lessons from the EU Experience in the United States

Although the European experience is instructive, the EU regulatory system cannot be transferred verbatim to the U.S. legal and political environment. For example, the primary legislation on which the EU system depends is, by U.S. standards, very short and succinct. This is in part because the European Commission, which drafts the legislation, is also ultimately responsible for the approval of biotechnology

products. The guidance documents that are key to the European approval system were already under development before the legislation was adopted, and all parties knew how the process would work. Under the U.S. system of separation of powers, Congress must provide more specific instructions to FDA if it wishes to achieve a result similar to that in the EU. It is for this reason that most provisions of U.S. drug law enacted in recent years are far more prescriptive than their counterparts in Europe. The provisions of the Hatch-Waxman Act governing abbreviated new drug applications are, for example, much more detailed than counterpart provisions in EU law governing generic marketing authorization applications. Similarly, for innovative products, Congress has mandated a specific type of evidence of effectiveness ("adequate and well-controlled clinical investigations"), while EU law contains only a general requirement for proof of efficacy. (This standard for proof of effectiveness, established in U.S. law under section 505 of the Federal Food, Drug, and Cosmetic Act, is equally applicable to biologics, because of provisions in relevant legislation providing for harmonization of approval requirements for drugs and biologics.)

Action-forcing mechanisms and dedicated funding may also be appropriate to ensure that FDA has the incentive and resources to develop guidance documents in consultation with relevant stakeholders. A new advisory committee may be appropriate to provide the kind of independent expert advice that the EMEA receives from the expert working party within the CHMP and from national authorities around the EU.

Nor should the United States assume that the data exclusivity period recognized in EU law provides the incentives required in the U.S. marketplace. Congress determined in 1984 that, in order to provide adequate incentives for research and development of important new medicines, the appropriate period of market exclusivity for pharmaceutical products should be approximately 14 years (the maximum effective life for a patent extended under the Hatch-Waxman Act). A strong case can be made for a similar period of data exclusivity in any approval system for biosimilars, because, as noted above, patents alone are unlikely to provide the certainty and predictability required for investments needed to bring new biotechnology products to market.

4. H.R. 1038 -- "The Access to Life-Saving Medicine Act"

Advocates of H.R. 1038 -- the "Access to Life-Saving Medicine Act" -- have suggested that the bill takes account of the EU experience. Unfortunately, in almost every important respect, the bill takes an approach that departs significantly from that taken in Europe, and from the basic principles that should govern any legislative framework for biosimilars. For example, H.R. 1038:

- Provides no mechanism for public comment or participation in the development of requirements for approval of biosimilars. Instead, requirements would be determined in private license application proceedings between individual applicants and FDA, and the bill actually includes provisions to discourage efforts

by innovative companies and other interested persons to bring scientific data and information to the Agency's attention.

- Does not require clinical testing of biosimilar products. In fact, the bill contains provisions that are intended to discourage FDA from requiring such tests.
- Requires FDA to treat the active substances of biosimilars as "highly similar" to reference products when their structural features are actually significantly different, and even permits FDA to approve follow-on products that are not deemed "comparable" to reference products on which they rely.
- Limits FDA's power to require post-market testing of biosimilars to detect rare but serious adverse events, including immunogenicity, that cannot be detected in pre-market testing.
- Requires FDA to make interchangeability determinations without first conducting public proceedings to determine what the requirements should be, and even if the Agency has not yet decided that such determinations are scientifically possible.
- Provides no period of protection for valuable safety and effectiveness data submitted by innovators. Follow-on applications, relying on innovators' data, could be filed immediately after innovative products are approved.
- Makes one-sided changes in the patent laws that favor follow-on applicants at the expense of innovators, including provisions for compulsory licensing under innovator patents.

Conclusion

In conclusion, I would urge the Committee to give careful consideration to the European experience in developing any pathway for follow-on biological products in the United States. Whatever model is chosen, however, it must protect patient safety and preserve incentives for research and development of new therapies. The United States today is the undisputed world leader in biotechnology-derived medicines. Congress should aim to ensure that any legislation creating a pathway for follow-on biologics does not undermine our leadership position.

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BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

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 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

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[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.

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 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]

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[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 (continued...)

First, because of current limitations of patentability of naturally 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

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other technologies. 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.

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 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] Further, new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.[6] Yet, as described below in more detail, it is well established that the costs and risks of developing biotech products are generally higher than for drugs. For example, average clinical development

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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*).

times for biologics have been found to exceed development times for small molecule drugs.[7] 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.

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.

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[7] Tufts Center for the Study of Drug Development. http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69

[8] Grossmann, Martin. Entrepreneurship in Biotechnology, Physica-Verlag NewYork, 2003.

- 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]

    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*

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[9] Grabowski, Henry, Iain Cockburn and Genia Long. "The Market for Follow-On Biologics: How Will It Evolve?" Health Affairs, 25(5).

[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.

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
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	4.1

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:

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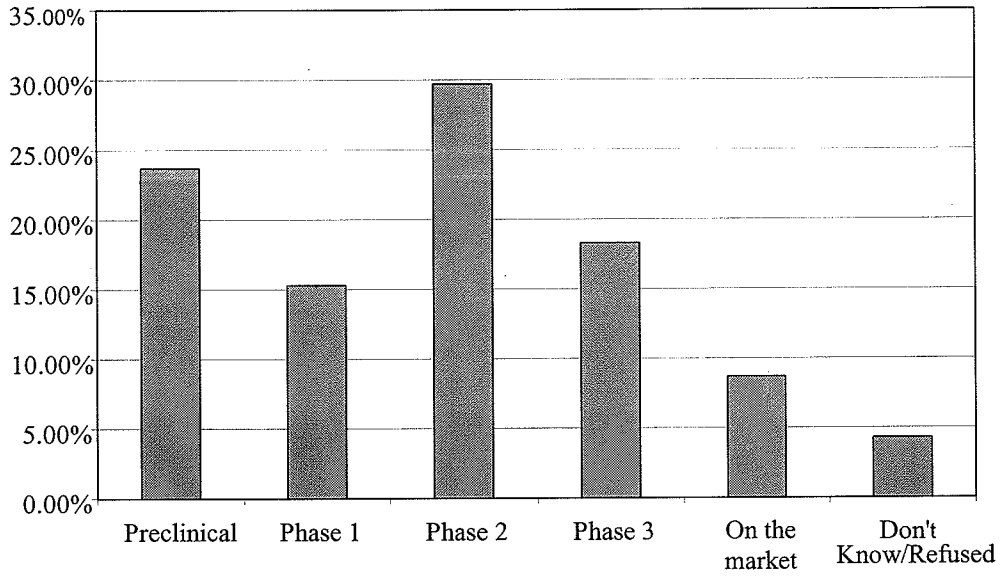
[14] The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

[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.

Latest Phase of Lead Product Development



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.

A. 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.