



## **A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY<sup>1</sup> 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 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

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<sup>1</sup> 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.<sup>2</sup> First, because of current limitations of patentability of naturally

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<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.

<sup>3</sup> Manheim, Granahan, and Dow. “‘Follow-On Biologics’: Ensuring Continued Innovation in the Biotechnology Industry,” *Health Affairs*, March/April 2006.

<sup>4</sup> 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.<sup>5</sup> Further, new molecular entities, on average, are marketed in the U.S. for 13.5 years before the entry of generic competition.<sup>6</sup> 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 times for biologics have been found to exceed development times for small molecule drugs.<sup>7</sup> 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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<sup>5</sup> 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.”

<sup>6</sup> Grabowski, Henry and Margaret Kyle. “Generic Competition and Market Exclusivity Periods in Pharmaceuticals,” *Managerial and Decision Economics* (forthcoming).

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

## **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%.<sup>8</sup>

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<sup>9</sup>

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<sup>8</sup> Grossmann, Martin. *Entrepreneurship in Biotechnology*, Physica-Verlag New York, 2003.

<sup>9</sup> 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.<sup>10</sup>

- Manufacturing Uncertainties: Biologics manufacturing necessitates far more planning, investment and skilled personnel and, thus, can be much riskier than small-molecule manufacturing.<sup>11</sup> “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.”<sup>12</sup>
- 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 products was 54% to 58%.<sup>13</sup> 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.*<sup>14</sup>

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:<sup>15,16</sup>

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<sup>10</sup> U.S. Bancorp Piper Jaffrey. “The Road Ahead for Biologics Manufacturing,” January 1, 2002.

<sup>11</sup> Lakshmikanthan, Jayant. “Outsourcing: Biologics Manufacturing: The CMO Advantage,” International BioPharm, Feb. 1, 2007.

<sup>12</sup> Webster, Christopher, et al. “Can There Be an Abbreviated Applications, Generics or Follow-On Products?” BioPharm International, July 2003.

<sup>13</sup> Parexel’s Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.

<sup>14</sup> The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

<sup>15</sup> Ernst and Young LLP, Annual biotechnology industry reports, 1995 – 2006. Financial data based primarily on fiscal-year financial statements of publicly traded companies.

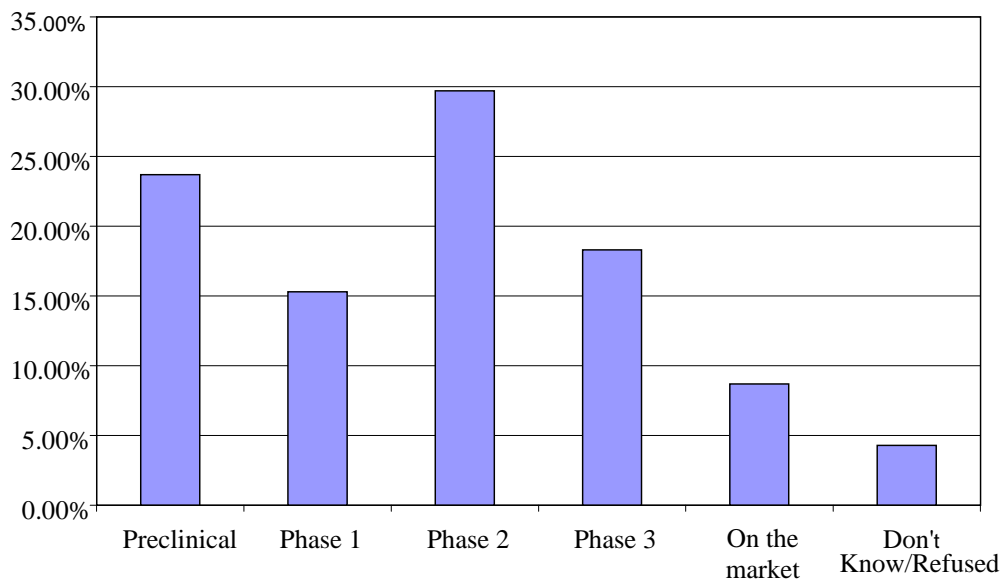
<sup>16</sup> Only about 20 biotech companies are currently profitable: Parexel’s Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
<b>Net Loss (\$B)</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:

**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.<sup>17</sup> 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.

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<sup>17</sup> 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.