



## Data Exclusivity for Biologics: What Is the Appropriate Period of Protection?

By Henry Grabowski

*Innovators of biologics need to have a period of market exclusivity long enough to allow them to earn an appropriate return on investment. Failure to safeguard a place in the market for these originators may reduce the number of new therapies created and could serve as a disincentive for innovators to expend resources improving existing biologics. As Congress considers legislation that would allow imitative biological products, known as “biosimilars,” to rely on the safety and efficacy data of original innovators, it must ensure that any provisions passed will foster, not stifle, discovery.*

Biologics are large, complex molecules derived from cell cultures, and they have provided medical breakthroughs for various cancers, multiple sclerosis, rheumatoid arthritis, and other conditions in recent years. There are currently more than 600 biologics in clinical trials for different indications, of which more than 250 target cancers.<sup>1</sup> The U.S. biopharmaceutical industry has been the global leader in biological advances for more than two decades.<sup>2</sup>

The innovator biologic market process is characterized by long discovery and development times, high failure rates, and increasing preclinical and clinical trial investment expenditures. The average clinical development times for new biologics have steadily increased to 108 months in 2005–2006 compared to 66 months in the first half of the 1990s.<sup>3</sup> Investments in discovering and developing a single new biologic (including the cost of failures and cost of capital) are now estimated at over a billion dollars with an increasingly focused Food and Drug Administration (FDA) requiring more, not less, investment prior to

approval.<sup>4</sup> Given these high upfront costs, data exclusivity is designed to provide a sufficient period of in-market exclusivity to encourage innovation when patent protection is limited or uncertain in value.

### Key points in this Outlook:

- Data exclusivity and patent protection play complementary roles in protecting innovators of biologics.
- Included in the major health reform legislation are provisions (supported by the Obama administration) that would limit the data exclusivity period for innovators to five to seven years.
- Twelve years or more of exclusivity will maintain incentives for future medical breakthroughs. If the data exclusivity period is too short, biotech firms may elect to invest in lower risk biosimilars rather than to pioneer innovative products.
- Smaller early-stage innovative firms will be most adversely affected, given their higher costs of capital.

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In the United States, most biologics are regulated under the Public Health Service Act. When patents on a biologic expire, the Public Health Service Act does not provide a way for competing versions of a biologic to enter the market without repeating the crucial clinical trials the FDA relied upon when approving the pioneer drug. This is in contrast with traditional “small molecule” drugs, for which the Hatch-Waxman Act allows generic manufacturers to enter the market very quickly upon patent expiration, mainly by piggybacking on the pioneer manufacturer’s clinical trial data—a so-called abbreviated filing to the FDA. In enacting a pathway for biosimilars, Congress must balance the dual objectives of cost savings with continued incentives for the development of novel biological therapies.

One of the most contentious issues is the data exclusivity period for a new biologic (also called the data protection period). This is the period after a new product’s approval before an imitative product can rely on the innovative firm’s safety and efficacy data to enter the market with an abbreviated filing. This is relevant when there is little patent life after FDA approval, which can happen for a variety of reasons. For small molecule drugs, the Hatch-Waxman Act provides for five years of base data exclusivity and a stay on generic entry of up to thirty months in cases when the product is still subject to patent challenge. Patent challenges by generic firms have become rampant in recent years, and almost all commercially successful drugs are subject to patent challenges early in their product life cycles.<sup>5</sup> The costly litigation process is problematic and needs to be resolved, as it leaves producers uncertain about the length of time new drugs will have patent protection. Given that patents in biologics are often narrower in scope and subject to more uncertainty than those for small molecule drugs, the length of the data exclusivity period has become a particularly important issue in the deliberations over an abbreviated pathway for biosimilars.

Congressmen Henry Waxman (D-Calif.) and Nathan Deal (R-Ga.) have introduced a biosimilars—or “follow-on biologics”—bill in the House that would allow for only five years of base data exclusivity for biologics (and would provide data exclusivity only when none of the major components of the biologic had been approved earlier). This is actually less protection than for small molecule drugs, because the bill does not include a stay for products undergoing patent challenges. However, a twelve-year exclusivity provision amendment to the main health reform bill in the House (HR 3200), cosponsored by

Anna Eshoo (D-Calif.), Jay Inslee (D-Wash.), and Joe Barton (R-Tex.), passed late in July. In the meantime, the Senate Committee on Health, Education, Labor, and Pensions’s health reform legislation also provides for twelve years of data exclusivity. The Obama administration, in turn, has suggested that a seven-year exclusivity period would be a “generous” compromise on this issue.

Advocates of the shorter five- to seven-year data exclusivity period generally argue that patent protection and market conditions will be sufficient to encourage innovation incentives for new biologics. They further claim that a longer data exclusivity period will provide excessive monopoly protection for innovators that would unnecessarily delay health sector cost savings and deter innovators from making significant improvements on their products that would be stimulated by competition from biosimilars. These, and related arguments, are advanced in a recent Federal Trade Commission (FTC) report on biosimilars, which also concludes that data exclusivity is unnecessary for innovation in biologics except in the rare cases in which no patent protection is available.<sup>6</sup>

## **The Complementary Roles of Data Exclusivity and Patent Protection**

Patents are awarded for inventions that satisfy the U.S. Patent and Trademark Office’s criteria for novelty, usefulness, and nonobviousness. Data exclusivity recognizes the long, costly, and risky process involved in generating the clinical trial and other data necessary to gain FDA approval after patents are filed. Both forms of protection address the need for innovators to have some period of returns before imitators can enter the market with an abbreviated filing. The life of a patent begins at the date of patent filing (generally prior to the beginning of clinical testing), while data exclusivity begins at the date of FDA marketing approval. From the date of approval, data exclusivity runs concurrently with patent protection and only provides additional market exclusivity (defined as the period of time before a biosimilar enters the market) when development was particularly long, resulting in little remaining patent life by the time the product reaches the market, or when biosimilar manufacturers are able to overturn or “work around” the innovator’s patents successfully prior to their expiration.

Patents may provide less clear and less predictable intellectual property protection for biologics than for small molecule drugs. Biologics rely on multiple patents,

including narrower product patents and process patents that may be more vulnerable to inventing around than small molecule product patents.<sup>7</sup> This is particularly so given that an abbreviated approval for biologics will be based on “similarity” rather than the sameness criterion used for small molecule drugs. Hence, it is possible that biosimilars may be different enough not to infringe on patents, but similar enough to qualify for an abbreviated approval pathway.

Data exclusivity provisions are therefore designed to reduce uncertainty and provide some stability and predictability for developers and investors against costly litigation and early patent disruption. They also provide an important incentive for products that spend a long time in basic research or clinical development after their core patents are filed. Novel products with new modes of action in particular often have lengthy discovery and development periods. Data exclusivity also encourages innovators to continue research and development (R&D) for new indications. This postapproval research is an important pathway in biologics for enhancing patient health and welfare.

## The Market for Biosimilars Will Expand

The FTC report also maintains that limited entry by biosimilars and advantages of being first to the market will insulate innovators’ revenues from biosimilar competition. Biosimilar entry will be costlier than generic entry, and biosimilar products are not likely to be interchangeable with branded ones for the foreseeable future. Given these factors, the report postulates that innovators can expect to retain 70–90 percent of the market in competition with biosimilars.<sup>8</sup> This prognosis of low market impact of biosimilars fails to consider the potential effects of technological and regulatory advances that will lower the costs of entry and payer responses that will increase market acceptance of biosimilars, however.<sup>9</sup>

Just as in the case of Hatch-Waxman and generic drugs, there will be a significant learning effect by public and private payers, physicians, and patients, resulting in increasing adoption of biosimilars. Many payers have begun to apply access and use controls to branded biologics, encouraging greater price-based competition. Rather than replicating the current level of payer controls for biologics (as suggested by the FTC report), the trend toward stronger payer management will greatly accelerate with the availability of biosimilars, which will facilitate direct price comparison. There is a strong

incentive to do this on cost-savings grounds, and payers are likely to have a central role in shaping the competitive impact of biosimilars. (See, for instance, the recently released MedPAC report suggesting ways in which the Medicare program could achieve savings from the existence of biosimilars.)<sup>10</sup>

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Given that biosimilars will operate in a global marketplace, there are also economies of scale and scope that can be realized by prospective entrants to the U. S. market. Europe is ahead of the United States in approving biosimilars for products like epoetin alpha, the largest selling biotech product, used to treat anemia for patients undergoing dialysis, chemotherapy, and treatments for AIDS. Assuming continued positive experiences there, this is likely to facilitate both regulatory and provider acceptance in the United States. Recent evidence with biosimilar entry in Germany for epoetin alpha also suggests that the FTC report’s assumptions on biosimilar share and price may already be outdated. Contrary to the FTC’s statements about European experiences with biosimilars, approximately 50 percent of the epoetin alpha molecule market had transitioned to corresponding biosimilars by the end of December 2008.<sup>11</sup> Similar outcomes can be expected in the United States over time as the market for biosimilars evolves on both the demand and supply side.<sup>12</sup>

## Data Protection Does Not Hurt Innovation

Biologics are characterized by vigorous competition across innovative firms with respect to the introduction of therapeutic alternatives and advances.<sup>13</sup> Multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate receptor site or enzyme. For example, there are many biologics currently in Phase II or III trials for breast cancer targeting the HER-2 receptor, a gene that has been shown to make cancers more aggressive when it is overexpressed, and related proteins downstream from HER-2. Similar

competition occurs in the TNF-inhibitors for rheumatoid arthritis (these medications target the inflammatory response associated with tumor necrosis factors) and the angiogenesis-inhibiting drugs for cancer. Because the level of unmet medical need is so high in these categories, there is vigorous competition by multiple manufacturers to achieve greater levels of clinical effectiveness. An innovative firm cannot simply rely on the status quo in the face of this dynamic competition from other innovative firms.

Postapproval research programs may also yield many clinically significant improvements, particularly in the form of additional approved indications, which were not established at the time of launch. Some important examples include the following:

- Herceptin, originally approved for metastatic breast cancer, was later approved for adjuvant use in early-stage cancer and may prove to be even more valuable there;
- Avastin was approved originally for colorectal cancer, and subsequently for lung cancer and breast cancer;
- Some of the approved therapies for rheumatoid arthritis later proved effective against other autoimmune conditions, from Chron's disease to psoriasis.

It is actually the risk of rapid entry from imitators using an abbreviated filing that could deter a firm from making postapproval R&D investments in new indications. This results from the potential of biosimilar firms to gain most of the associated economic benefits from important new indications without incurring any of the R&D costs for the additional clinical trials.

## Relevant Benchmarks Exist

The average market exclusivity period for small molecule drugs in the United States is approximately twelve years. This value is determined primarily by the length of time needed for R&D, patent filings, and the outcome of patent challenges. The average market exclusivity period for small molecule drugs has been relatively stable, declining slightly since 2000. At the same time, the speed of generic penetration after initial introduction has increased dramatically, with generics typically capturing most of the market within a few months of first generic

entry.<sup>14</sup> In addition, there is a much higher probability now than there was a decade ago that drugs will experience patent challenges and that they will occur much sooner after brand launch.<sup>15</sup> This could adversely impact innovation incentives in the coming years.

In the European Union, both small molecule drugs and biologics now receive ten years of data exclusivity plus one additional year for a new indication (increased from six years in several member countries). A key basis for this change was the recognition that the United States has been the dominant source of innovation in pharmaceuticals, and the exclusivity period was increased to encourage the development of a more innovative European industry.

Previously, the National Academies of Sciences and Engineering analyzed the relevant issues and called for a data exclusivity period in the United States at least equal to the European Union's period of ten to eleven years for large and small molecule drugs. It also called for additional research into whether this period is adequate given the complexity of and length of time required for drug development.<sup>16</sup>

## Economic Analyses Can Provide Insights

In a peer-reviewed article in the scientific journal *Nature Reviews: Drug Discovery*, and expanded upon in an academic white paper, I propose a model for analyzing the economic factors affecting long-term investment incentives for innovative biologics.<sup>17</sup> The model uses a "break-even" approach, which calculates the period of time necessary for a representative portfolio of biologic candidates to earn an investment return equal to its cost of capital. Without the prospect of earning returns at least equal to a firm's cost of capital, investors will not provide the funds to engage in costly clinical trials for promising therapeutic candidates. The model adopts a "sensitivity analysis" approach, considering the outcomes for a range of plausible assumptions on various parameters including the data exclusivity period. This work builds on my prior analyses of R&D costs and returns in pharmaceuticals, which has been used by government agencies such as the Congressional Budget Office to assess the impact of public policies on pharmaceutical innovation.<sup>18</sup>

Under a plausible set of assumptions I find that short (five- to seven-year) exclusivity periods do not allow investors to earn necessary returns within normal product life cycles for biopharmaceuticals. In particular, with a short data exclusivity period, only extremely favorable

combinations of parameters allow the portfolio to earn returns equal to or above the company's cost of capital within time periods of two decades or more. When data exclusivity periods increase to twelve years or more, positive expectations on returns are obtained for many different combinations of parameter values over normal product life cycles.<sup>19</sup>

One of the key insights of this model is that it accounts for the sensitivity of investment returns to the firm's cost of capital. This is relevant because small, early-stage biotechnology companies experience much higher costs of capital than larger, self-financed companies.<sup>20</sup> Sensitivity in the *Nature* model to alternative cost-of-capital assumptions indicates that limited data exclusivity periods will negatively impact small, early-stage biotechnology companies disproportionately. The biotech "investment ecosystem" today is driven by hundreds of start-ups funded by venture capital and private equity. It has been estimated that venture-backed firms represent 40 percent of biotech employment.<sup>21</sup> Most ventures are early-stage (fewer than 10 percent have a product on the market), small (65 percent have fewer than fifty employees), and never turn a profit.<sup>22</sup> Given the potentially far-reaching effects of policies affecting R&D investment programs and industry structure, Congress should proceed carefully in selecting data exclusivity periods.

## Conclusion

As Congress crafts an abbreviated regulatory pathway for biosimilars to encourage more price competition, it must maintain incentives for future medical breakthroughs with a data exclusivity period that adequately recognizes the long and costly R&D process for new biologics. Data exclusivity periods of twelve years or more provide an "insurance policy" to stimulate innovation in cases in which effective patent protection is limited in scope or time, or uncertain in nature. If the data exclusivity period is only a nominal five to seven years, many products with limited patent protection, regardless of clinical value and importance to patients, will not enjoy sufficient exclusivity time to recover R&D costs and earn positive returns. Smaller, early-stage innovative firms will be most adversely affected, given their dependence on external financing with high costs of capital. Furthermore, biotech firms may elect more often to invest in lower-risk biosimilar manufacturing opportunities, rather than to pursue innovative pioneer positions. The net result would be a shift from an aggressively innovative industry to an imitative one.

## Notes

1. Pharmaceutical Research and Manufacturers of America, "Medicines in Development," *Biotechnology* (2008), available at [www.phrma.org/images/110308%20biotech%202008.pdf](http://www.phrma.org/images/110308%20biotech%202008.pdf) (accessed August 17, 2009).

2. Henry Grabowski and Richard Wang, "The Quantity and Quality of Worldwide New Drug Introductions 1992–2003," *Health Affairs* 25, no. 2 (2006): 452–60.

3. Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition." *Nature Reviews: Drug Discovery* 7 (2008): 479–88.

4. Joseph DiMasi and Henry Grabowski, "The Cost of Pharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 28 (2007): 469–79.

5. For a recent analysis of patent challenges, see Henry Grabowski, Margaret Kyle, Genia Long, Richard Mortimer, and Noam Kirson, "Evolution of Market Exclusivity Periods, Paragraph IV Challenges and Generic Penetration" (unpublished manuscript, July 2009). The authors find that on a sales-weighted basis, over 90 percent of the small molecule products subject to generic competition are experiencing patent challenges, and these are occurring relatively early in the product life cycle. Under the Hatch-Waxman Act, so-called paragraph IV filings can begin four years after the innovator's product is approved by the FDA. Many of the bills for biologics would allow patent challenges to occur immediately upon approval; they would also allow significant time in advance of expiration of the data exclusivity period for a biosimilar to apply for conditional approval through an abbreviated filing at the FDA, enabling preapproved biosimilars to enter the market more quickly after the data exclusivity period ends.

6. Michael S. Wroblewski and others, *Emerging Health Care Issues: Follow-on Biologic Drug Competition* (Washington, DC: Federal Trade Commission, June 2009), available at [www.ftc.gov/os/2009/06/P083901biologicsreport.pdf](http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf) (accessed August 18, 2009).

7. Bruce Manheim, Patricia Granahon, and Kenneth Dow, "Follow-on Biologics: Ensuring Continued Innovation in the Biotechnology Industry," *Health Affairs* 25, no. 2 (2006): 394–404.

8. Michael S. Wroblewski and others, *Emerging Health Care Issues*, 10–23.

9. Professor Richard Frank of Harvard University, in a presentation to the Office of Health Economics conference on biosimilars, indicated there are now between fifteen and thirty partnerships and firms currently developing biosimilar products for various worldwide markets. He also indicated that India and China are investing heavily in manufacturing infrastructure in FDA-approvable facilities with variable costs that appear much

lower than for European Union or U.S. facilities. See Richard Frank, "How Much Price Competition Can We Expect from Biosimilars?" (lecture, Office of Health Economics, London, UK, June 2, 2009).

10. Medicare Payment Advisory Commission (MedPac), *Report to the Congress: Improving Incentives in the Medicare Program* (Washington, DC: MedPac, June 2009), available at [www.medpac.gov/documents/Jun09\\_EntireReport.pdf](http://www.medpac.gov/documents/Jun09_EntireReport.pdf) (accessed August 18, 2009).

11. Hospira, Inc., "Hospira Responses to FTC Questions on Biosimilars," May 19, 2009, available at [www.ftc.gov/os/comments/healthcarecompissues/090519hospirasupplementonbiosimilars.pdf](http://www.ftc.gov/os/comments/healthcarecompissues/090519hospirasupplementonbiosimilars.pdf) (accessed August 18, 2009). This is based on sales of standard units of biosimilar drugs referencing Erypo (the branded version of epoetin alpha in Germany) as tracked by IMS Health. Epoetin alpha biosimilars totaled 54 percent of the market for the molecule on a standard unit basis as of December 2008.

12. Dr. Steven Miller, of Express Scripts, Inc., postulated at a recent Health Industry Forum in Washington, D.C. that U.S. market penetration for biosimilars can be expected to be comparable to or exceed that of Germany, given the greater array of managed care instruments available to influence physician and patent choices in this country. Steven Miller, "Potential Impacts of Biosimilars in the U.S. Market" (discussant, Health Industry Forum, Washington, DC, June 11, 2009).

13. See John E. Calfee, "When Patents Are Not Enough: Data Exclusivity for Follow-on Biologics," *Health Policy Outlook* no. 10 (December 2008), available at [www.aei.org/outlook/29022](http://www.aei.org/outlook/29022), for a discussion of the dynamics of biologic competition and many of the examples cited here.

14. Henry Grabowski and Margaret Kyle, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 28 (2007): 491–502. This paper also found that patent challenges have had a significant negative influence on the market exclusivity periods for small molecule drugs. Under Hatch-Waxman, there is a five-year data exclusivity period. However, the filing of an abbreviated new drug application with a patent challenge is subject to an additional thirty-month stay to allow for court resolution of the dispute. If the issue is still unresolved, the generic firm can enter at its own risk after the thirty-month stay has expired.

15. Henry Grabowski, Margaret Kyle, Richard Mortimer, Genia Long, and Noam Kirson, "Evolution of Market Exclusivity Periods."

16. Committee on Prospering in the Global Economy of the 21st Century: An Agenda for American Science and Technology, Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, and Institute of Medicine, *Rising Above the Gathering Storm: Energizing and Employing America for a Brighter*

*Economic Future* (Washington, DC: National Academies Press, 2007).

17. Henry Grabowski, "Follow-on Biologics." For an extension of these results to incorporate the effects of data exclusivity limitations on average break-even periods, see also Henry Grabowski, Genia Long, and Richard Mortimer, "Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques" (working paper no. 2008-10, 2008), available at [www.econ.duke.edu/Papers/PDF/Data\\_Exclusivity\\_Periods\\_for\\_Biologics.pdf](http://www.econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf) (accessed August 18, 2009).

18. See, for example, Congressional Budget Office (CBO), *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, A CBO Study* (Washington, DC: The Congress of the United States, 1998) available at [www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf](http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf) (accessed August 18, 2009); and CBO, *How Health Care Reform Affects Pharmaceutical Research and Development, A CBO Study* (Washington DC: The Congress of the United States, 1994), available at [www.cbo.gov/ftpdocs/48xx/doc4846/EntireReport.pdf](http://www.cbo.gov/ftpdocs/48xx/doc4846/EntireReport.pdf) (accessed August 18, 2009).

19. Henry Grabowski, Genia Long, and Richard Mortimer, "Data Exclusivity Periods for Biologics." Alex Brill has modified the investment returns model but with assumptions on the cost of capital and contribution margin that are not representative of most biotech firms. See Alex Brill, "Proper Duration of Data Exclusivity for Generic Biologics: A Critique" (unpublished manuscript, November 2008). The issues raised by his analyses and differences with my own work are discussed in Henry Grabowski, Genia Long, and Richard Mortimer, "Data Exclusivity Periods for Biologics." See also the recent analysis on the cost of capital for privately financed biotech firms in Iain Cockburn and Josh Lerner, "The Cost of Capital for Early Stage Biotechnology Ventures," slideshow, National Venture Capital Association (2009), available at [www.slideshare.net/NVCA/the-cost-of-capital-for-early-stage-biotechnology-ventures](http://www.slideshare.net/NVCA/the-cost-of-capital-for-early-stage-biotechnology-ventures) (accessed August 18, 2009).

20. For further discussion and analyses of the role of venture capital and representative values for the cost of capital for privately financed biotech firms, see Ian Cockburn and Josh Lerner, "The Cost of Capital for Early Stage Biotechnology Ventures."

21. Lawton Burns, Michael Housman, and Charles Robinson, "Market Entry and Exit by Biotech and Device Companies Funded by Venture Capital," *Health Affairs* 28, no. 1 (2009).

22. Biotechnology Industry Organization, "A Follow-on Biologics Regime without Strong Data Exclusivity Will Stifle the Development of New Medicines" (2007): 7, available at [www.bio.org/healthcare/followonbkg/FOBS\\_final\\_20070827.pdf](http://www.bio.org/healthcare/followonbkg/FOBS_final_20070827.pdf) (accessed August 19, 2009).