Data Exclusivity Is Key to Maintaining Continued Innovation in Biologics

Biologics are revolutionizing health care with effective, targeted therapies. For example, biologics have produced dramatic progress against many cancers, and biologic medicines being researched today are looked to for the needed advances against such diseases as Alzheimer's and Parkinson's. The biologic Herceptin, which treats an aggressive form of breast cancer, has been credited as potentially leading to a "dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure."[1] The potential benefits of continued advances in biotech medicines are evident from projections of what could be achieved by new treatments that delay the onset or slow the progression of Alzheimer's disease. According to a study by the Lewin Group, within five years of discovery of a breakthrough treatment for Alzheimer's disease, projected annual Medicare spending would decline by $51 billion.[2]

As new biologics have the potential to fundamentally change the course of many diseases, it is critical that any legislation authorizing an abbreviated pathway for follow-on biologics (FOBs) appropriately balance the incentives to develop new medicines—and the opportunity for better health outcomes and overall cost savings this offers—with the interest in savings through entry of FOBs into the marketplace. A base period of exclusivity of 14 years plus a significant additional period of exclusivity for new indications is key to achieving this balance.

Biologics Are Achieving Breakthrough Medical Advances

In addition to breakthroughs due to new medicines, a leading pattern for achieving treatment advances with biologics is research that leads to new uses of medicines that have already been approved by the U.S. Food and Drug Administration (FDA). As an example, one biologic has been labeled "a mini-pipeline all by itself," with "some 20 clinical trials under way for different cancers or stages of cancer."[3] The 2007 American Society of Clinical Oncology (ASCO) meeting highlighted a number of important advances against cancer achieved through research identifying new uses for already approved biologics. For example, researchers at the ASCO meeting cited how the biologic Erbitux, originally approved for colon cancer, was approved for two new indications to treat head and neck cancer. The FDA characterized these new indications as "important advances in the treatment of head and neck cancer because it has been shown to help some patients live longer."[4] Such achievements demonstrate the importance of maintaining incentives in order to ensure investment in research and development (R&D) into new biologics and continued research post-approval leading to new indications.

Congress Is Considering Legislation to Create an Abbreviated Pathway for Follow-on Biologics

Legislation has been introduced that would create an abbreviated process for FDA approval of FOBs. FOBs would be similar to but not exact copies of biologics developed by innovator companies. Experts predict that FOBs are likely to have lower R&D costs than innovator biologics and to potentially yield modest savings over the cost of the innovator biologic it is intended to model.[5] The lower R&D costs would be due to proposed legislation allowing follow-on manufacturers to rely in part on safety and efficacy data developed by innovator companies to gain approval of the original or "reference" products. Recent estimates suggest potential cost savings to the federal government of no more than $200-280 million a year,[6] though savings are unlikely to materialize within the first five years after legislation is enacted.[7] Any legislation creating an abbreviated pathway for FOBs should include a balance between generating potential cost savings and ensuring incentives that promote the continued development of biologics capable of continuing the rapid advance against disease. Data exclusivity is one key incentive for maintaining robust R&D.

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Data Exclusivity Is a Key Incentive for Drug Discovery

Data exclusivity is a type of intellectual property, distinct from patent rights. In effect, it prevents other manufacturers from using an innovator's data to gain FDA approval of the manufacturers' products for a fixed period of time. The purpose of data exclusivity is to provide continued incentives for the investment essential to the development of new biologics. If an innovator's data could be used by another company to gain approval for a similar biologic early in the innovator product's lifecycle, innovators may not be able to recover the more than $1.2 billion average cost of biotech medicine development.[8] Their ability to earn a return or break even could be undercut by companies that do not bear the substantial risks and costs of R&D leading to new biologics.

Data exclusivity would not create a monopoly for a biologic to treat a particular condition or manufacture a kind of medicine. Many biologics now compete with other biotech medicines and pharmaceuticals, and this would continue to be the case. For example, one class of biologics used to treat rheumatoid arthritis comprises at least four biologics,[9] each approved on the basis of original clinical trials by an innovator company. Data exclusivity would only prohibit using the data developed by another company to gain approval of an FOB for a specified period of time.

Data Exclusivity Works in Conjunction with Patents

Patents are an important form of intellectual property, but are not themselves sufficient to create the environment needed to support large-scale investment in biologic discoveries. Patent protection is often less robust for biologics than for small molecule drugs. Many biologic patents are process patents or relatively narrowly drawn product patents. These may be susceptible to work-arounds, especially under a regulatory regime that permits FOBs to differ in their structural features from innovator products. Furthermore, if a biologic's development time is extended, there may be a very limited period of patent protection remaining once a product is approved. Therefore, data exclusivity is critical to providing a measure of certainty needed to support robust investment by assuring that an innovator's safety and effectiveness data cannot be used to gain FDA approval of a similar biologic while "working around" its patents.

Cost and Risks Characteristic of Biotech Innovation Require Strong Data Exclusivity

Strong data exclusivity is important to fueling the development of new biologics because innovation is costly and risky. Data exclusivity offers a consistent, reliable period that offers a company the potential to earn a return on the investment in drug discovery that can help keep resources flowing to biologics R&D.

Large R&D investments must be made long before FDA approval and with uncertainty about post-approval patent challenges. The safety and efficacy data that must be provided by innovator companies to gain FDA approval of a biologic can take more than a decade to compile and conservatively require an average of more than $1.2 billion in pre-approval R&D.[10] The estimates do not include the additional $250 to $450 million or more that innovator companies often spend on manufacturing facilities, which can take three to five years or more to construct.[11] (For example, publicly reported cost estimates by two companies for building a manufacturing facility were $660 million and $2 billion, respectively.[12])

These investments are, of course, made with no guarantee of return. A biologic may fail to gain FDA approval —it has been reported that the overall probability of success in clinical development is 30 percent. Biologics also have had lower success rates in the most expensive Phase III trials, indicating that biologics that fail in clinical trials do so only after high development costs have been incurred.[13] In the first half of 2007, only one biologic license application (BLA) for a new biologic has been approved by the FDA, which is considered a testament to the complexity of the challenges involved in developing biologics.[14] Biologics may not be profitable even if they are approved—of the 30 new biologics introduced between 1982 and 1994, six comprised about 70 percent of total sales in 2002, with many of the remaining 24 biologics likely not recouping their R&D costs.[15]

Adding to the uncertainty of achieving returns on investment is the possibility that few successful biologics will be subject to patent challenges from FOBs early in their lifecycle but after all of the investments in R&D and manufacturing facilities have been made. This would shift the odds against such large-scale, speculative investment. Strong data exclusivity recognizes the need to allow for a return on risky investments to counter the disincentive to such investments that FOBs would otherwise cause.

The biotechnology sector as a whole has earned little or no profits. The biotechnology sector has generated enormous expenditures on biologics discovery, but little profitability. This highlights how important it is that any legislation to create an abbreviated pathway for FOB approval must include strong incentives, with data exclusivity as one such incentive, for promoting drug discovery—and the health care improvements and cost savings that can bring.

Harvard Business School professor Gary Pisano reports that between 1975 and 2004 biotech revenues grew but profitability remained flat and profit levels "essentially hover close to zero throughout the life of the industry."[16] Biotechnology has been characterized as "one of the biggest money-losing industries in the history of mankind….," losing nearly $100 billion since 1976.[17] The New York Times reports that only 54 of the 342 publicly traded biotech U.S. companies were profitable in 2006.[18] Many biotech companies have been in business for over 20 years and are not profitable.[19] For example, Xoma, a small biotech started in 1981, has yet to earn an operating profit or to market a drug of its own, yet it has expended $700 million raised from investors and other pharmaceutical companies. OSI Pharmaceuticals expects to break even for the first time in 2007, after having lost $1.3 billion since 1983.[20] According to one analyst, "[I]t is virtually impossible to find other historical examples, at least at the industry level, for which such a large fraction of new entrants can be expected to endure such prolonged periods of losses and for which the vast majority may never become viable economic entities."[21] In light of these facts, strong data exclusivity would be a key basis for continued investment in the biotech sector because it creates an opportunity for an adequate return on investment for those few medicines that do make it through the R&D process and gain FDA approval.

Biotech R&D often relies on venture capital, requiring strong data exclusivity to ensure continued investment. The biotech sector is highly reliant on venture capital. Biotech companies are able to attract venture capital and other investments, even though many projects and companies lose money.[22, 23] This is based on the chance that if a company beats the long odds against it and gains FDA approval of a biologic it has the potential to earn a return on its investment that will compensate for the many losses.[24] The potential to earn a return on the few biologics that are profitable would be greatly reduced with the introduction of FOBs without significant data exclusivity that (1) allows a biologic to be on the market for a significant period before an FOB can be approved based on the innovator's data and (2) protects against the uncertainties caused by patent challenges early in a product's life (but long after R&D investments are made). Lack of such protections would potentially lead venture capital to shift away from biotech discovery.[25]

- **Congress Should Set Data Exclusivity at 14 Years for Newly Approved Biologics with a Significant Additional Period for Biologics that Gain a New FDA-Approved Indication**

Fourteen years of data exclusivity are needed to create the opportunity to break even on R&D investment. Analysis by Duke University economist Henry Grabowski provides an estimate of the time necessary for a model portfolio of biologics to earn a positive risk-adjusted return on capital (the money used to fund a business) and recoup the large upfront R&D investment needed to develop a new medicine. The paper reports that this "breakeven lifetime" is between 12.9 and 16.2 years, assuming discount rates of 11.5 percent and 12.5 percent, respectively. That is, 12.9 years is based on an 11.5 percent cost of capital, which increases to 16.2 years if the cost of capital is 12.5 percent. This is the range of discount rates that Grabowski's prior research

has shown applies to established biotech companies.* The breakeven lifetime is the basis for the length of data exclusivity needed to sustain investment in biologics R&D.[26]** Thus, a data exclusivity period shorter than 14 years would multiply uncertainties about potential returns and the risk that products could not achieve a positive return, driving venture capital and other investment away from supporting the discovery of new biologics.

The 13- to 16-year breakeven period is conservative. First, it assumes a cost of capital applicable to companies that already have approved biologics on the market. The cost of capital would likely be higher—and thus the breakeven period longer—for companies that do not already have an approved product. Second, it excludes the costs of post-market R&D on new indications, which are discussed below. Third, it excludes the cost of post-marketing commitments, which further delays time to potentially break even. These post-approval commitments may include randomized clinical studies or the creation of a prospective, multi-center registry for biologics patients that includes clinical evaluations of patients in the registry and the submission of comprehensive annual reports for a substantial period.

When Congress created the pathway for approval of generic small molecule drugs, it understood the need to create a policy that balanced the promotion of cost savings and the need to ensure incentives for innovation. A 1984 House of Representatives report indicates that Congress limited the restored patent term to no more than 14 years after marketing in order that "research intensive companies will have the necessary incentive to increase their research and development activities."[27]

A significant additional period of data exclusivity should be provided for biologics that gain FDA approval for new indications. Many biologics are approved initially for a single disease. However, a key characteristic of biologics is their potential to play a role in treating a range of different conditions.[28] Continued research into new indications often occurs long after approval of the initial indication. It may take several years to achieve FDA approval of a new indication and involve the full array of clinical trials. (Of course, because of the pioneering nature of research on new indications, many trials fail and not all post-approval research results in a new indication.)

AEI scholar John Calfee reports that "the most important advances in treatment are from products that have been on the market for a while but whose properties were not completely understood until intensive research after the drug was introduced.…Rituxan, for example, which was found to treat rheumatoid arthritis, was originally approved for a form of non-Hodgkin's lymphoma, and Enbrel (psoriasis) and Remicade (Crohn's disease) were originally approved for rheumatoid arthritis."[29] Researchers at the 2007 ASCO annual meeting discussed promising findings from a number of studies into new uses for currently approved biologics and predicted that in the future there will be more of a focus on targeting approved biologics and determining which other diseases or conditions and patient groups are most likely to benefit from their use.[30] Of course, trials occurring now, should they prove successful, would not result in an approved new use for several years, meaning that the chance to earn a return on the investment in developing a new indication is uncertain and often many years off.

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*The cost of capital is often used as the discount rate, the rate at which projected future cash flow will be discounted for inflation and financing charges, to give a net present value (NPV). NPV is a standard method for the financial appraisal of long-term projects. Used widely throughout economics, it measures the value of a future cash flow in terms of the amount of money today that would be equal in value to the projected future cash flow. For an investment to be worthwhile, the projected return on investment must be higher than the cost of capital.

**As discussed in prior work by Grabowski, while a few biologics may have shorter break-even periods due to high sales, many biologics will have longer break-even periods due to lower sales. In fact, a small share of biologics comprises the large majority of the return on investment for all biologics. This indicates the importance of establishing a data exclusivity period that offers an opportunity to attract investment across the full range of research projects.

Unless a company can have confidence of the potential to recoup investment in the research and clinical trials needed to gain new indications, its capacity to support this important way of expanding medical knowledge and developing new and better treatments of serious illness would be greatly diminished. Therefore, data exclusivity is a key incentive for the research needed to develop new indications for biologics. In addition to data exclusivity available for initial approval of a new biologic, those biologics that gain FDA approval of a new indication should receive a significant additional period of data exclusivity for the biologic as an incentive for the significant continuing research investment post-approval.

CONCLUSION

With new biologics looked to for fundamental advances in medical care against a range of serious illnesses, it is critical that any legislation to develop an abbreviated pathway for FOBs appropriately balances the development of new medicines—and the potential for better health care outcomes and overall cost savings this offers—with the interest in savings through FOBs. Establishing a base period of exclusivity of 14 years plus a significant additional period of exclusivity for new indications is critical to achieving this balance.

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