



When Patents Are Not Enough: Data Exclusivity for Follow-On Biologics

By John E. Calfee

Congress is expected to pass legislation regarding follow-on versions of biologics in 2009. These pathbreaking drugs to treat cancer and other diseases are extremely complex and may need postdiscovery protection if their patents quickly succumb to legal challenges. Most of the major legislative proposals in the 110th Congress provided data exclusivity for twelve to sixteen years. In approaching the issue, Congress should act cautiously, relying on a few basic principles that do not suppress research and development (R&D) in this vital sector.

Our patent system is awash in controversy. Critics charge that patents have been so easily granted and are so murky in their details that pervasive litigation and other problems make the system more costly than it is worth (Bessen and Meurer 2008). The leading exception is the pharmaceutical industry, which provides a classic example of the virtues of the patent system. Without a patent system and the temporary protection from competition by imitators it provides, developers of new drugs would have little prospect of collecting the profits necessary to motivate innovative research. Even so, a fundamental tension lies at the core of intellectual property for pharmaceuticals. The traditional role of the patent system is to reward the *discovery* of new inventions. But in the pharmaceutical industry, probably more than in any other, what most needs rewarding is *postdiscovery* research. Only after a compound has been discovered, isolated, and patented can a firm mount the increasingly long, complex, and expensive clinical trials necessary to obtain Food and Drug Administration (FDA) approval to place a drug on the market and begin to collect revenues and, eventually, profits.

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When a patent expires for most pioneer drugs, other firms can quickly enter the market with generic versions, pushing down prices and largely eliminating profits for the pioneering firm. Fast entry occurs because the 1984 Hatch-Waxman Act relieved generic firms of the requirement to run their own clinical trials to demonstrate safety and efficacy. Instead, as long as they can demonstrate that the drugs enter the relevant parts of the body in essentially the same way the pioneer drug does, they can rely upon pioneer firms' clinical data when applying for FDA approval to market generic versions of the same molecule.

And then there is a special type of drug known as "biologics." These substances are grown rather than isolated or synthesized, as traditional chemicals or "small molecule" drugs are. Vaccines were once the dominant form of biologics, but the advent of biotechnology has led to many highly innovative biologics, from natural enzymes (such as human growth hormone) to chimeric monoclonal antibodies (biotech-engineered humanized variants of naturally occurring but rare proteins that are used to treat a wide range of illnesses, including cancer, rheumatoid arthritis, and multiple sclerosis).

Biologics Are Different

Biologics involve several practical differences from traditional drugs. An obvious one is that they are exceedingly complex to create and manufacture, so much so that the FDA and others have emphasized that products from different manufacturing facilities may differ significantly in therapeutic and side-effect profiles (Woodcock 2007; Woodcock, Griffin, et al. 2007). This will have to be taken into account in any follow-on biologic legislation. Other differences are less obvious but of great importance, especially in connection to intellectual property.

Postapproval Research. Newer biologics usually target highly specific biological mechanisms that are themselves the subject of continuing research. Although traditional small-molecule drugs sometimes have well-defined biological targets, biotechnology drugs are typically designed and researched at a much deeper scientific level. One result is that research on a modern biologic is often still in a relatively early stage at the time of FDA approval. This much-remarked phenomenon has been described in considerable detail (Grabowski 2008; Calfee and DuPré 2006; Calfee 2007a; Bernstein 2006). A striking feature of such postapproval research is in the delineation of new indications, which can range from variants of the same illnesses (lung cancer in addition to colorectal cancer) to completely different conditions (cancer instead of rheumatoid arthritis). Of course, small-molecule drugs have also been the subject of important postapproval research. Notable examples include beta blockers and the statin class of cholesterol-reducing drugs.

For modern targeted therapeutics, however, the postapproval research agenda apparently occurs more quickly, ranges more widely, and shows no signs of nearing an end for some of the most prominent drugs. This reflects the fact that at the time a novel biologic is approved, little may be known of what that drug can do or of what can be achieved in connection with its biological target. This is clear from a few striking examples. Herceptin, a monoclonal antibody approved in 2004 for late-stage breast cancer, was found to be even more valuable for early-stage cancer and may prove effective for an unexpected range of genetic abnormalities (Calfee 2007a). Avastin, approved in February 2004 for colorectal cancer, in October 2006 for lung cancer, and in February 2008 for breast cancer, is the subject of probably more than one hundred ongoing clinical trials of varying complexity. Rituximab, a monoclonal antibody that suppresses

the CD20 protein, was originally approved for non-Hodgkin lymphoma and was later approved for rheumatoid arthritis. Subsequent trials have revealed striking effectiveness against multiple sclerosis (Hauser et al. 2008), and it is being explored for and sometimes used to treat lupus, idiopathic thrombocytopenia purpura, and chronic lymphocytic leukemia and other autoimmune diseases (Sailler 2008). Velcade, approved in 2003 for multiple myeloma after years of difficult research, was approved in 2006 for lymphoma and in 2008 for a different stage of multiple myeloma and is or has been the subject of more than three hundred trials (Ward 2008). Tumor necrosis factor (TNF) inhibitors such as Enbrel have been approved for rheumatoid arthritis and several other conditions. Ongoing research suggests that the anti-inflammatory properties of TNF inhibitors may allow those drugs to delay the onset of Alzheimer's disease and reduce the risk of coronary heart disease, at least in rheumatoid arthritis patients (van Vollenhoven 2008).

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Competition via "Inventing Around." The dynamics of targeted biologics research creates competitive modes that are increasingly important but often neglected in public discussion. Enhanced competition occurs in two ways. One is a consequence of the fact that drugs' targets are often complex, involving a cascade of biological events that may be interruptible at various points in addition to the point at which a pioneer drug operates. This opens the door for competing firms to "invent around" a pioneer drug by devising a completely different biologic to address the same target (Calfee and DuPré 2006). Competition can arrive with surprising speed, as happened with the TNF inhibitors and some of the cancer drugs described earlier, such as Avastin, which inhibits the vascular endothelial growth factor (VEGF) protein and was the first approved drug to rely upon antiangiogenesis (that is, inhibiting the growth of new arteries to feed cancer cells). This success has already inspired several firms to develop VEGF inhibitors, and some have been approved (Flanagan 2006; Million 2008).

Crossover Competition. A second mode of competition arises from the fact that a single targeted biological mechanism may operate in varied ways and at multiple locations within the body. As postapproval research explores a drug's targeted mechanism and the drug's effects on that mechanism, the drug may turn out to be useful for a condition that is already treated by a competing drug, perhaps one aimed at a different target. In this "crossover" form of competition, new indications for drugs originally approved for nonoverlapping indications come to compete with each other. TNF inhibitors, originally developed for rheumatoid arthritis, are used against Crohn's disease and psoriasis, causing TNF inhibitors to compete with other drugs for which those conditions are indicated. The multiple sclerosis drug Tysabri may soon have competition from Rituxan (Hauser et al. 2008), while Tysabri has itself been approved to treat Crohn's disease. Epidermal growth factor receptor (EGFR) antagonists are another example. This class includes both large-molecule monoclonal antibodies and small-molecule inhibitors of tyrosine kinases. Four drugs (Tarceva, Iressa, Erbitux, and Vectibix) have been approved by the FDA for a variety of cancers, including non-small cell lung, colorectal, head and neck, and pancreatic (Ciardiello and Tortora 2008). Again, some of the new indications are bound to cause drugs to compete with each other.

Biologics, Patents, and Postpatent Competition.

Another important difference between biologics and older drugs lies in patents. Although many biologics involve numerous patents instead of just one or a few bedrock patents, the patents undergirding biologics are often more complex and subject to changing legal standards. They are therefore more susceptible to legal challenge than patents for small-molecule drugs (Grabowski 2008). This creates the possibility of a market dynamic in which generic manufacturers can observe research on a promising biologic and, if the drug finally meets success and obtains FDA approval, quickly launch patent challenges, which, if successful, would open the door to competition from nonpioneer products.

Finally, traditional drugs differ from biologics in another fundamental way: except for a few relatively simple older biologics, the law does not offer a simple pathway, comparable to the Hatch-Waxman process, through which generic manufacturers can enter the market by basing their FDA applications on the clinical data accumulated by the pioneer firms.

Toward Follow-On Biologic Legislation

The rapidly increasing role of modern biologics in both medical treatment and health care costs has prompted vigorous debate over whether and how to construct some sort of Hatch-Waxman-like process for "biosimilars" (the European Union's term), "follow-on proteins" (the FDA's preferred term), or "follow-on biologics." Those terms are more accurate than "generic biologics," as few if any follow-on biologics would permit the simple interchangeability of pioneer and follow-on drugs that is familiar in the small-molecule world.

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The Central Role of Data Exclusivity. Congress is widely expected to pass a follow-on biologics law in 2009. Much recent discussion has focused on the crucial topic of "data exclusivity." This is something that is applied when patents have expired or are about to expire. The period of data exclusivity would determine how long a follow-on firm must wait before using the pioneer firm's clinical data to support its application to the FDA to approve a follow-on biologic. For the rare small molecule whose patent expires before or shortly after a new drug is approved, the Hatch-Waxman Act provides the pioneer firm with five years of data exclusivity. The effect is to provide pioneer firms with at least five years of exclusive marketing before facing competition.

Data exclusivity promises to be more important for biologics than it has ever been for small-molecule drugs. Because patents of newly approved biologics may prove more open to challenge than small-molecule patents, new biologics could be subject to competition shortly after initial FDA approval if there is no period of data exclusivity. Should early patent challenges and early follow-on entry become a real possibility, such a prospect would be taken into account in planning future biologic R&D, with obvious adverse consequences for R&D investment.

The EU is farther along than the United States in dealing with follow-ons and data exclusivity. The EU has already approved several follow-on versions of older and simpler biologics and has constructed a law to govern the approval of follow-ons for newer, more complex

biologics. That law provides for ten years of data exclusivity, with an additional year for new indications approved within eight years of initial approval (Grabowski 2008; Woodcock et al. 2007).

Several follow-on biologic bills have been circulated in Congress. S 1695, sponsored by Senators Edward Kennedy (D-Mass.), Mike Enzi (R-Wyo.), Orrin Hatch (R-Utah), and Hillary Clinton (D-N.Y.), would provide twelve years of data exclusivity. S 1505, sponsored by Senator Judd Gregg (R-N.H.), would provide twelve to sixteen years. HR 1956, sponsored by Representative Jay Inslee (D-Wash.) with support from the Biotechnology Industry Organization, a trade group, would provide twelve to fifteen years; HR 5629, sponsored by Representatives Anna Eshoo (D-Calif.) and Joe Barton (R-Tex.), would provide twelve to fourteen years. However, HR 1038, sponsored by Representative Henry Waxman (D-Calif.), would provide no data exclusivity at all.

The Problem of Setting Data Exclusivity Periods. How long should data exclusivity be? For years, economists have debated the analogous question for patents, arriving only at the conclusion that it all depends on many factors and that there is no reason why patent length should be the same for every industry. Nor is there a solid foundation for setting different periods for different industries. For the time being, a unitary system prevails in which the same rules apply to all industries. But data exclusivity is a tool that comes into play when patents fail to provide reasonable protection for innovation. Data exclusivity is arguably more important for modern biologics than for any other industry, and we have to think afresh about exclusivity and how it works in this unusual industry. Given the stakes—a substantial amount of future R&D hangs in the balance—Congress should exercise an abundance of caution in designing follow-on biologic legislation so as not to endanger valuable future research.

One approach to data exclusivity is to examine the record of biologics approved in the past decade or two and estimate how long it took for those products to generate profits after taking account of the time and expense of R&D and the risks of failure (DiMasi and Grabowski 2007). Working with those data and assuming that postapproval research increases financial outlays by 35 percent, Grabowski (2008) estimated payback periods of between 12.9 and 16.2 years depending on the cost of capital (which, in his model, ranged between 11.5 percent and 12.5 percent). Such results might serve as a guide to a suitable period of data exclusivity.

This approach is fraught with peril. Aside from a possibly nonrepresentative sample, the exercise involves numerous assumptions about the cost of capital, profit margins, and prices after the first follow-on enters the market. Reasonable changes to these assumptions can easily affect the results by 30–40 percent (Brill 2008). Another almost insuperable difficulty is how to take reasonable account of the financial risks in biotechnology R&D, in which most products and, indeed, most firms fail before realizing any revenues at all, not to mention profits. Furthermore, one of the most fundamental characteristics of biologics—the dominant role of postapproval R&D—is highly variable and is impossible to predict in terms of either costs or medical value. In particular, because the drugs with the most promising postapproval R&D agendas have reached the market only in the past few years, there is no way to extrapolate from recent experience in order to estimate the future volume, costs, and medical value of postapproval R&D expenditures—although it is already clear that, for many of the most valuable biologics, those expenses will be large relative to initial R&D and will continue for many years.

A Sensible Approach to Data Exclusivity

What makes sense is to rely on a few basic principles and a deep sense of caution about the threat of suppressing R&D. A signal consideration is that if Congress errs by establishing too short a period for data exclusivity, the R&D it suppresses will never be observed, nor will the products that the missing R&D would have created. Also important to thinking about data exclusivity is the remarkable speed of inventing around in many biotech-based biologic drug classes and the vigor of crossover competition, which are causing biologics markets to be surprisingly competitive, partly as a byproduct of postapproval research.

In thinking about how long data exclusivity should last, a useful starting point is the exclusivity period typically created by patents. Although patent law provides for twenty years from the time a patent is filed, the research-intensive pathway to FDA approval tends to leave perhaps ten to twelve years of postapproval patent life. That relatively brief period has to generate—at least on average—sufficient revenues and profits to encourage firms to pursue more research in search of molecules, few of which will ever show a profit (DiMasi, Hansen, and Grabowski 2003). The market's strong record in providing broad benefits from postapproval research in competitive therapeutic classes, such as

statins, suggests that lengthy research agendas are often extremely beneficial. This in turn suggests that when there is just one drug in an innovative therapeutic class, limits on patent life may suppress valuable research on the class. Although there has been considerable debate over some of the tactics that pharmaceutical firms use near the end of patent life, such as developing variants that are sufficiently attractive to keep some patients from switching to generic versions of the original drug, there seems to be very little evidence that patent-based exclusivity for small-molecule drugs is too long.

Grabowski (2008) reports that in his sample of biologics, development times increased almost linearly from the early 1980s, reaching more than nine years for drugs approved in 2005–2006, leaving less than eleven years of postapproval patent life. That hardly seems excessive, if it were the determining factor in practical marketing exclusivity. There are sound reasons for thinking that modern biologics provide so many benefits from post-approval research extending over many years that exclusivity, whether provided by patents or data exclusivity provisions, should be at least as long as for small-molecule drugs. The fact that some of the same scientific attributes of biologics that generate extended research streams also generate vigorous competition among drugs in a class and across classes suggests that the social losses from providing for fairly long exclusivity periods (twelve to fourteen years) would be small compared to what are likely to be substantial social gains from exclusivity.

An earlier version of this *Health Policy Outlook* incorrectly characterized the approval status of the pharmaceutical Rituximab and misidentified the year Avastin was approved to treat breast cancer. We regret the errors.

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