



Facing Reality on Follow-On Biologics

By John E. Calfee

New and highly sophisticated biotech drugs called biologics have enjoyed unprecedented success in fighting disease. The law does not provide a way to create generic versions of these complex and expensive drugs after patents expire. This reflects current science, as generics in the traditional sense of bioequivalence are practically impossible. Congress, however, appears poised to create a regulatory pathway for “follow-on biologics.” This would involve reduced testing requirements while granting the Food and Drug Administration (FDA) wide discretion on exactly what to require. There is no reason to expect a reasonable follow-on biologic law to bring dramatic cuts in health-care spending as claimed. But unless Congress is careful, it will interrupt long-term drug research programs and reduce incentives to develop new biologics.

Practically all drugs fall into two categories: small molecules and large molecules, the latter of which are usually called biologics. Most of the drugs we take on a daily basis, such as Lipitor, Prilosec, and Lexapro, are small molecules. When the patent for a small-molecule drug expires, generic manufacturers enter the market to sell exactly the same molecule. Then competition works its magic, bringing plunging prices, health-care spending cuts, and the refrain, “Is there a generic version of that drug?” At the heart of this arrangement lies interchangeability based on bioequivalence, which is another way of saying that branded and generic versions of the same drug are so alike that one can be exchanged for the other without harm to the patient. That is why generic manufacturers are not required to run clinical trials before getting FDA approval to enter the market. And that, in turn, is why generic versions arrive so quickly and prices fall so rapidly after patent expiration (CBO 1998).

This system was created by the 1984 Hatch-Waxman Act, which increased the generic share of prescriptions from less than 20 percent to more than half by 2000 while drastically reducing prices

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(CBO 1998, PhRMA 2001, Milne and Cairns 2003). Under the new Medicare Part D drug benefit, the generic share of prescriptions is 60 percent (CMS 2007). No other industrialized nation has come close to matching this record in terms of either price or market share over the past two decades.

Large Molecules are Different

But Hatch-Waxman was a small-molecule law. It had nothing to say about biologics like Epogen, Procrit, and Aranesp for anemia; Enbrel and Remicade for rheumatoid arthritis; and Avastin and Herceptin for cancer. These and other biologics are transforming one therapeutic area after another, starting with side effects from chemotherapy and moving on to tackle cancer itself, rheumatoid arthritis, and much more. And not so incidentally, these products are capturing a growing chunk of our health-care spending, now accounting for some \$50 billion annually. None of them face generic competition when their patents expire.

Many people, among them Representative Henry Waxman (D-Calif.), want to do something about that. They seek a law like Hatch-Waxman

for biologics. Many proponents, such as AARP and pharmacy benefit managers like Express Scripts and Caremark, which negotiate drug prices for insurance firms, claim that such a law would dramatically reduce drug prices. They are wrong, but to see why, we have to look at how a new biologics law would actually work.

The leading legislative proposals (H.R. 1038 and S. 623, collectively known as the “Access to Life-Saving Medicine Act”) would create a regulatory pathway for unpatented “follow-on biologics” (FOBs, the FDA’s term) or “biosimilars” (the European Union’s term). But it would not introduce widespread production of generics in the usual sense. This reflects the science. Unlike small-molecule drugs, which are synthesized using chemical methods, most biologics are highly complex proteins grown in living systems (some consisting of several such components). Some of them are actually produced in mammalian cells from DNA that has been modified to cause the expression of substances unique to humans rather than to, say, the mouse in which the essential agent was originally isolated. The final product cannot be described in simple terms. A humanized mouse-derived monoclonal antibody like Avastin is best seen as the output of a multistage gestational process. The end result depends strongly on the minutiae of that process itself, meaning that the “generic” that comes from a new biologic manufacturing facility may not work the same way as drugs that patients have been using for years. Most of these products are far too complicated and varied for a simple test to determine whether the outputs from two different facilities are bioequivalent or will at least have identical therapeutic effects. As technology advances, however, the ability to make such determinations will become more feasible for a growing portion of the biologic world. But subtleties such as protein folding, which can strongly alter a biologic’s effect in the body, will make that goal elusive for some time.

The biologics market will likely never resemble the simple world of traditional generics. Interchangeability in the usual sense will be uncommon, and it will have to be supported by far more data than is required for small-molecule generics. Do not expect to hear your pharmacist say, “Oops, I almost forgot to mention that I’m giving you the generic version of that monoclonal antibody your doctor prescribed.” This is not to say we should dispense entirely with the idea of streamlined regulations for FOBs. Like most economists, I favor limited patent life and limited periods of market exclusivity

based upon those patents. But we have to be realistic about what to expect.

FDA and Physician Discretion

If a follow-on biologic law is passed this year, it will almost certainly grant the FDA a great deal of discretion in setting approval standards. H.R. 1038 makes FDA approval of an FOB the default option if the applicant meets specified standards for data on “comparability,” and again by default, comparable products are to be regulated as being “interchangeable,” more or less like traditional generics. In both cases, however, the bill grants the FDA the power to require more data if it is not satisfied that the follow-on would really work in the same way. In stipulating such default options, the bill’s sponsors are whistling in the dark. There is little prospect that the default option will be the usual choice. As written, the bill’s comparability standards for protein products allow for minor differences in an amino acid sequence, or structural differences caused by “post-translational events” or “infidelity of translation or transcription.” But even a single switch in an amino acid can make a large therapeutic difference, and “translation” involves modifications (perhaps in the way the protein attaches to other molecules) that may be essential to its operation. Many other seemingly tiny disparities in a biologic can arouse the body’s incredibly sensitive immune system with significant or even drastic adverse effects. The FDA staff and the medical community at large are aware of these facts. There is every reason to think that in practice, the FDA will ignore the default standard and develop its own data requirements for FOB approvals.

What can we expect the FDA to do, given that a blanket “no-clinical trials” standard is not feasible for these drugs? This is not entirely new territory for the FDA (Manheim, Granahan, and Dow 2006; Usdin 2002, 2005; Woodcock 2007). Certain first-generation biologics such as insulins and hormones were approved through the same regulatory apparatus as small molecules, and thus qualify for the Hatch-Waxman regimen. For such products, the FDA uses an informal sliding scale. It requires varying amounts of animal and human clinical trial data to be reasonably sure that the new product will work much like the older one for which it will provide also an alternative, but it also requires much less than that used for clinical proof of safety and efficacy. As their focus moves to a newer generation of biologics such as

Epogen and Neupogen (which treat the side effects of kidney failure and cancer chemotherapy, respectively), FDA staff will probably require more clinical trial data while still stopping far short of traditional standards for safety and efficacy.

This will plunge the FDA deep into the balancing of risks and benefits that involve large, varying degrees of uncertainty simply because of the intrinsic nature of biologics manufacturing and testing. The FDA will bring to this task its innate aversion to risk in approving new drugs (Calfee et al. 2007). Two and a half years of vitriolic criticism of the FDA about the safety of Vioxx, selective serotonin reuptake inhibitor antidepressants, and other drugs, reinforced by a high-profile Institute of Medicine report (IOM 2006), have undoubtedly made the FDA more risk-averse than ever. This will surely figure into decisions about FOBs, many of which will pose all sorts of alarming possibilities. Moreover, many of the FDA's most vigorous critics on drug safety are the same people who now urge Congress to let the FDA determine what standards to apply when approving FOBs. These critics will watch closely for unexpected safety problems with those follow-ons. We can therefore expect the delineation of regulatory standards to occupy a couple of years or more, followed by additional years of regulatory deliberations as the various applicant biologics proceed through whatever levels of testing the FDA chooses to require.

All this applies especially to the monoclonal antibodies and other extraordinary new biotech drugs that happen to be very effective, very expensive by traditional standards, and of nearly unrivaled complexity. It will be many years before any sort of follow-ons for these drugs appear, regardless of patent expirations. Fortunately, "inventing around"—the creation of entirely new drugs that exploit a proven biological target—is proceeding with amazing speed, rapidly providing alternatives to many breakthrough therapies (Calfee and DuPré 2006). Competition without generics is emerging, although its nature has yet to be revealed.

Even if the FDA is not excessively cautious in permitting FOBs to enter the market, there is the matter of what doctors and patients will do. Compared to payers and academic thought leaders, doctors have always been the toughest sell for generic drugs. When choosing between a branded pioneer biologic and a quasi-generic of uncertain bioequivalence, doctors have been exceptionally reluctant to switch. This is evident from the long-running debate over Synthroid and other thyroid

hormone preparations (Gibaldi 2005). We can expect similar caution with FOBs, especially the most complicated and expensive ones, such as monoclonal antibodies, which account for many of the "miracle drugs" to hit the market in the past five years, with striking effects on patient health and, increasingly, insurance spending.

Follow-On Biologics and Health-Care Spending

A few organizations have estimated that passage of a FOB law will bring large health-care cost savings. This is unlikely. A report from Express Scripts (Miller and Houts 2007) simply assumes that past generic-entry and pricing patterns will apply to biologics. That assumption will not hold, at least not in the first five to ten years of the FOB era, which means that the projected savings will not come to pass. In a Pharmaceutical Care Management Association report, the bulk of the projected savings comes from just three related drugs: Epogen and Procrit (the same drug sold under different names for different uses), Aranesp (an improved version of Epogen), and Neupogen (PCMA 2007). We may indeed get follow-ons of these drugs after a few years, but the follow-ons will almost certainly have to undergo significant clinical work, will be few in number, will be far more costly than small molecules to manufacture, and will probably be offered at only modestly reduced costs (15–25 percent, as is typical of initial generics in traditional small-molecule markets). Moreover, physicians will not easily be persuaded to switch from the drugs they trust to follow-ons. Their patients may be even more suspicious about safety and efficacy. Given the vast differences between traditional generics and FOBs, there is little reason to think that legislation to create a new regulatory pathway for biologics will significantly cut health-care costs in the near future.

Intellectual Property

The full name of the Hatch-Waxman Act is the Drug Price Competition and Patent Term Restoration Act of 1984. Despite its popular image as simply opening up the market for generics, the act was actually a much-celebrated compromise (CBO 1998). Pioneer drug manufacturers were granted de facto patent extensions in certain circumstances, such as when excessive FDA approval deliberations ate up an inordinate amount of patent life. Manufacturers were also given five years of "data exclusivity," meaning that regardless of patent

expirations, generic manufacturers had to wait five years after approval of a drug before making use of the underlying data which had typically been accumulated at great cost through clinical trials and other research. The European Union has gone further, granting roughly ten years of data exclusivity. In both cases, the data exclusivity clause is an escape valve designed to preserve research and development (R&D) incentives in case patents do not do the job.

One might think this is irrelevant for biologics. They are typically protected by many patents over various aspects of the main active agent, along with “process” patents that mainly cover manufacturing methods. But such process patents tend to be weaker than molecular patents, or at least more susceptible to challenge, leaving considerable uncertainty about when a profitable biologic would be subject to legal challenge and then competition from follow-ons. Molecular patents, which, like the drugs themselves, are sometimes technically complex, may also be more susceptible to challenge than traditional small-molecule patents.

We must take into account the unique research environment of biotech-created biologics. Many of the most valuable biologics, including the monoclonal antibodies that have given so much hope to cancer patients and others, are the results of extensive R&D agendas that have no obvious end (Calfee 2007, Calfee and DuPré 2006). Success against one cancer, for example, provides the foundation (scientific *and* financial) for additional clinical trials on other cancers. Avastin, approved in 2004 for colorectal cancer, is reportedly in trials for about twenty other cancers. Rituxan, first approved for cancer, has also been approved for rheumatoid arthritis; research no doubt continues in both areas and perhaps in others. Herceptin, approved for late-stage breast cancer, was demonstrated over several years of additional clinical trials to be even more valuable in fighting early-stage breast cancer. This research story, too, has no natural end.

Therefore, dispensing with data exclusivity—which the principal legislative FOB proposals do—is probably a dangerous course. In most cases, ordinary patent protection will suffice. But where it does not, the prospect of five or ten years of exclusive marketing rights may be the only strong incentive to pursue potentially fruitful new research on a biologic whose greatest value has yet to be ascertained.

AEI research assistant Elizabeth DuPré and editorial assistant Evan Sparks worked with Mr. Calfee to edit and produce this Health Policy Outlook.

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