During the past 30 years, advances in medicine and pharmaceutical research generated a new class of drugs called biologics. These drugs are complex proteins, carbohydrates, or other large molecules derived from biological sources (1). By contrast with more traditional pharmaceuticals (small-molecule drugs), biologics are not synthesized chemically from less complex components, but rather are derived from or manufactured using living organisms or extracted tissue (2).

Biologics make up a small but significant percentage of the overall pharmaceutical market. According to a 2009 Federal Trade Commission report, in 2007 American consumers spent ~$40 billion on biologics out of $287 billion spent for prescription drugs overall (3). Demand for biologics is also growing rapidly (3, 4).

Because of their complex nature and the laborious processes required to manufacture biologics, they usually are considerably more expensive than small-molecule drugs. The yearly cost for products such as Humira (used to treat arthritis) and Herceptin (used to treat breast cancer) monoclonal antibodies range from $12,000 to $48,000, respectively. As the first such drugs come off patent, clinicians and policymakers hope that generic versions (follow-on biologics or biosimilars) can be quickly brought to market to help reduce healthcare costs (3, 5). Entry of follow-on biologics into the US pharmaceutical market is likely to provide important cost savings for most healthcare consumers. But manufacturers, policymakers, and regulatory authorities must ensure that the economic benefits that biosimilars promise are not endangered by unique safety risks that follow-on biologics can pose.

**Promise and Peril**

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch–Waxman Act) established new regulatory processes designed to speed the review and approval of generic drugs (6). Since then, low-cost generic drugs have taken an increasingly larger share of the prescription-drug market. They accounted for >60% of the total market in 2007 (7) and have saved the US healthcare system an estimated $734 billion over 10 years (8). Under the Hatch–Waxman Act, the US Food and Drug Administration (FDA) does not require generic drug manufacturers to perform the same types of comprehensive safety and effectiveness tests as brand-name (innovator) pharmaceutical manufacturers (9). Instead, generic manufacturers can submit an abbreviated new drug application (ANDA) to demonstrate that their products are manufactured in accordance with current good manufacturing practices (CGMP) standards and “comparable to an innovator [brand-name] drug product in dosage, form, strength, route of administration, quality, performance characteristics, and intended use.”

Regulatory review and approval of generics is based on the fact that they are considered indistinguishable from brand-name pharmaceuticals in laboratory and clinical tests (10, 11). By contrast with small-molecule drugs, however, the source materials for many biologic drugs are genetically engineered, self-replicating eukaryotic or prokaryotic cell lines, which are often legally protected as intellectual property. Manufacturing processes are also often patented, so companies that plan to produce follow-on biologics must not only create their own source materials but also reverse-engineer the complex manufacturing processes used to isolate and purify these drugs. The complexity of biologic drugs and specificity of their source materials and manufacturing processes make it impossible for two such drugs to be...
The Hatch–Waxman Act was never designed to streamline the process of reviewing follow-on biologics

Ortho Biotech, replaced the human serum albumin used in processing with polysorbate 80 (Tween), which is a plant-based compound. Although Tween plays a similar role in the manufacturing process, it is biochemically distinct from human serum albumin. The investigation concluded that because of complex interactions between Tween and other ingredients, micelles formed within the final product, affecting the purity and triggering unforeseen immunogenic responses and intracranial hemorrhage in some users (19).

Elevated rates of epoetin-associated pure red-cell aplasia (PRCA) were also observed among patients treated with human serum albumin–free Procrit (20). Rates of PCRA ranged from six cases per 100,000 patient years to 18 cases per 100,000 patients years with and without human serum albumin, respectively. That is believed to be associated with the presence of organic compounds that leached the polysorbate detergent from the rubber stoppers on the storage vials (20, 21). The cases described here are not unique. In a study of 174 biologics approved for use in the United States and Europe, postmarketing concerns were raised for nearly a quarter of those drugs. Safety-related regulatory actions were issued for 41 biologics, including “black box” warnings on 19 (22).

A Need for Regulatory Reform

When the Hatch–Waxman Act was passed in 1984, most approved drugs on the market were small-molecule drugs. FDA approved the first biologic drug (recombinant insulin) in 1982. Only a handful of biologics were on the market when the ANDA process for streamlined generic drug review and approval was established. The Hatch–Waxman Act was never designed to streamline the process of reviewing follow-on biologics and, in fact, does not technically apply to the approval of such drugs. Whereas small-molecule drugs are regulated by the federal Food, Drug, and Cosmetic Act, most biologics are regulated under the Public Health Service Act. To date, however, the FDA has approved 10 follow-on biologics for

Example 2 — Procrit: In 2003, postmarketing studies of the safety and effectiveness of the antianemia drug Procrit (epoetin alfa, also known as Epogen or Eprex) showed that 16% of users had sudden, often fatal, reactions to the drug, with the most common cause of death being intracranial hemorrhage (16). Procrit is a recombinant version of the naturally occurring glycoprotein erythropoietin, which is produced naturally in human kidney and stimulates red blood cell development (17). In earlier trials in patients with cancer or chronic renal failure, <10% of users died (18), and the rate of death was no greater than that of participants not using the drug, with no case of intracranial hemorrhage observed. Researchers concluded that the likely cause of the increase in fatal interactions was a change in manufacturing procedures. Under pressure from the FDA and other international regulatory agencies to decrease the risk of contamination from HIV, Creutzfeldt-Jakob disease, or other pathogens, the manufacturer,
use in the United States under the ANDA provisions of the Food, Drug, and Cosmetic Act.

Until recently, the Public Health Service Act had no ANDA-like provision for expedited approval of follow-on biologics (23). However, Congress and the FDA were under intense pressure to develop a streamlined regulatory process for their review and approval, resulting in passage of the Biologics Price Competition and Innovation Act of 2009 (described below). A challenge remains, however, to create regulatory pathways that account for the unique nature of biologic drugs and the increased risks that they pose to patient safety (2).

Many critics have argued, for example, that follow-on drugs that would be otherwise marketed as identical to brand-name biologics could not rightfully be considered “generics” at all (2, 24). Because manufacturing and processing biologics is specific to each drug (and to the patentable source materials from which such drugs are derived), it was difficult see how follow-on biologics could be identical in ingredients, strength, dosage, formulation, route of administration, and activity to brand-name biologics (9, 25). Despite recent advances in techniques to manufacture, purify, and test biosimilars (such as new platform technologies to purify monoclonal antibodies), laboratory testing is not always adequate to prove bioequivalence.

Consider the differences between human interferon-β1a (INF-β1a; Avonex) and INF-β1b (Betaseron), biologics commonly used in treatment of multiple sclerosis (MS). Both types of interferon can be derived from the same source material (activated T-cells) and can be distinguished from one another on the basis of a few small structural differences (amino acid changes and posttranscriptional modifications) that arise during production and purification (26). Indeed, many in vitro tests cannot distinguish INF-β1a and INF-β1b (27), and clinical trials have shown that INF-β1b is less active than INF-β1a in vivo, thus requiring higher doses to achieve a therapeutic effect (28). INF-β1b is also more immunogenic than INF-β1a, showing a level of response associated with diminished therapeutic effect in MS patients (29).

In addition, as suggested previously, the safety of follow-on biologics cannot be predicted based solely on clinical experience with brand-name drugs (23). As the TGN412 trial results tragically demonstrate (30), laboratory and animal studies might not adequately assess the safety and efficacy of these drugs (1, 31).

Similarly, even a slight change in the source material or manufacturing process can alter significantly the safety and efficacy profile of biologic drugs, as seen during Procrit postmarketing surveillance (1, 16, 18).

**CURRENT REGULATIONS: THE EUROPEAN MEDICINES AGENCY**

The European Medicines Agency (EMA, formerly EMEA) was the first pharmaceutical regulatory authority to create guidelines specific to addressing the unique safety concerns represented by review and approval of biosimilars. Following the surprising INF-β1a and INF-β1b clinical trial results, and recognizing the lack of clear preclinical markers for biologic drug safety and efficacy, the EMA decided (in the short term) that follow-on biologics will not be reviewed using an expedited, ANDA-like process (32).

Because typical laboratory and animal bioequivalence tests are insufficient to show that brand-name and follow-on biologics are comparable, the EMA requires additional studies for generic review and approval, which can include assays characterizing postmanufacturing changes in drug structure or formulated dosage studies that compare safety and efficacy of a generic and a brand-name drug (32, 33). Many such studies are designed to look for differences in immunogenicity that may affect drug safety and efficacy, and more extensive testing is required for biosimilars that are more likely to trigger an immunological response, either because of their nature (e.g., monoclonal antibodies), their manufacture (e.g., interferons), or because of previously observed safety issues (e.g., epoetins). For example, to approve a biosimilar epoetin, the EMA not only requires that generic manufacturers show bioequivalence in laboratory and animal tests, but they also must conduct additional clinical safety and efficacy tests. These include single-dose safety tests in healthy volunteers and two randomized controlled tests of efficacy in renal patients (34).

The EMA may require generic manufacturers to conduct postmarketing studies looking for unanticipated safety and immunogenicity issues observed with approved brand-name biologics (32, 33). For example, with biosimilar epoetins, the EMA requires extensive postmarketing surveillance of all renal patients for evidence of elevated rates of epoetin-associated pure red-cell aplasia, as seen with lots of Procrit manufactured using polysorbate 80 instead of human serum albumin (20).

The EMA thus has created a regulatory structure in which all biosimilars undergo the same quality assurance, safety, and efficacy tests, but with additional pre- and postmarketing testing requirements that vary according to the class of biosimilar. For example, for those with “a chance that the immune response could seriously affect the endogenous protein and its unique biological function,” the EMA requires manufacturers to submit additional data from studies designed to characterize antibodies and their likely safety, efficacy, and pharmacokinetic impact (32). To date, the EMA has established additional test guidelines for several different product classes, including products containing biotechnology-derived proteins as an active substance, immunologicals such as vaccines and allergens, blood or plasma-derived products and their recombinant alternatives, and other biologics (such as gene or cell therapy products) (35).

The EMA’s cautious approach to the review and approval of biosimilars has been remarkably successful. To date, its regulatory process has been
used to approve several biosimilar drugs, including two generic versions of human growth hormone (BioPartners’ Valtropin and Sandoz’s Omnitrope products), five types of epoetin (Hexal’s Epoetin Alfa, Hospira’s Retocrit, Medice’s Abseamed, Sandoz’s Binocrit, and Stada’s Silapo products) and six generic versions of granulocyte colony-stimulating factor (CT Arzneimittel’s Biogratstim, Hexal’s Filgrasin Hecal, Ratiopharm’s Filgrasin rationpham and Ratiogristim, Sandoz’s Zarzio, and Teva’s Filgristim products). The EMA’s requirements for increased laboratory, animal, and clinical testing of biosimilars enabled researchers at Sandoz to detect a potentially dangerous change in product immunogenicity that occurred when production of Omnitrope was moved from one manufacturing facility to another (36, 37).

The EMA has also recommended rejection of several biosimilars, including BioPartners’ generic version of human interferon-α2a (Alpheon) and Marvel Life Sciences’ generic versions of human insulin. Although the former appeared to be functionally equivalent to brand name human interferon-α2a (Roferon-A), EMA regulators raised quality control concerns about its manufacturing process. In addition, clinical trials comparing Alpheon and Roferon-A for the treatment of hepatitis C showed higher rates of relapse and more frequent side effects in patients receiving the generic drug (38). Similar concerns were raised about the safety and efficacy of Marvel’s generic insulins, leading the India-based manufacturer to withdraw its European marketing application (39, 40).

**Current FDA Regulations**

The FDA is likely to establish a regulatory process similar to that of the EMA. Recently, as part of the Patient Protection and Affordable Care Act signed into law by President Obama in March 2010 (Public Law 111-148), the Public Health Service Act was amended to create an ANDA-like provision for expedited approval of follow-on biologics. Commonly referred to as the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), this statute allows generic drug manufacturers to seek FDA approval of biosimilar drugs if they can show similarity to an approved brand-name biologic based on laboratory, animal, and clinical studies of safety and efficacy.

Like the earlier EMA regulations, the BPCI Act requires that generic drug manufacturers conduct “a clinical study or studies (including immunogenicity, pharmacokinetics, or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency” of the follow-on drug (41). In addition, because pharmacists in the United States often dispense generic drug alternatives unless specifically ordered not to by prescribing physicians using “dispense as written (DAW)” codes, the BPCI Act also requires that manufacturers demonstrate that switching between a brand-name and follow-on biologic for treatment of chronic conditions poses no increased risk of side effects.

At the time this article was written, it remained unclear how the FDA planned to implement the statutory requirements of the BPCI Act. The FDA’s Biosimilar Implementation Committee recently held a two-day public hearing (2–3 November 2010) to seek input from interested stakeholders (including patient advocates, clinicians, and drug manufacturers). The meeting explored how to ensure that a new process for reviewing and approving biosimilar drugs could be done both efficiently and cost-effectively, with scientific rigor (75 Federal Register 192, 61497). Video and audio recordings of this hearing are available online at www.fda.gov/Drugs/NewsEvents/ucm221688.htm. Many concerns raised by public stakeholders at this meeting are the same as those described herein, namely how to ensure the safety and efficacy of follow-on biologics while allowing a streamlined review and approval process. New guidance from the FDA on this issue is expected in early 2011.

One way for the FDA to address safety and efficacy concerns that biosimilars pose would be to adopt a version of the current European regulatory pathway for the review and approval of follow-on biologic drugs. Such approach would be permissible under the statutory requirements of the BCPI Act. Admittedly, adopting a comparable pathway for review and approval of follow-on biologics in the United States might prove politically risky. Given current concerns about spiraling healthcare costs, any regulatory process that slows the review, approval, and marketing of low-cost follow-on biologics is likely to be unpopular with consumers, politicians, and generic drug manufacturers alike. Considering the growing importance of both generic and biologic drugs in the United States, however, decisive action is needed to ensure that follow-on biologics are safe and effective before they become available to consumers. Protecting the safety of patients must be the fundamental purpose of a pharmaceutical regulatory agency, regardless of the short-term political and economic consequences.

Part 2 of this article will discuss ethics issues related to the development and testing of biosimilars.

**References**


Amber W. Aagaard, MS, is a staff scientist at Teleflex Medical, 2917 Weck Drive Durham, NC 27703; aalwood@live.com; 1-607-346-6880. Serena Purdy is a graduate student in The Bioethics Program, Union Graduate College, 80 Nott Terrace Schenectady, NY 12308; serena.purdy@gmail.com; 1-905-876-8775. Corresponding author Sean Philpott, PhD, is director of research ethics for The Bioethics Program, Union Graduate College, 80 Nott Terrace, Schenectady, NY 12308; philpots@mail.uniongraduatecollege.edu; 1-202-247-5174