Like their pharmaceutical counterparts, biopharmaceutical innovators and manufacturers are concerned by the threat of generic competition. The complex statutory and regulatory scheme that governs the transition from a brand-controlled market to a generic-controlled market now requires pharmaceutical companies to coordinate, even orchestrate, the development of patent portfolios before the US Patent and Trademark Office (PTO), the approval of new drug applications by the US Food and Drug Administration, and the enforcement of and/or attack on those patent portfolios before federal courts. Although biopharmaceuticals are currently one step removed from generic entanglements, that situation may soon change.

This article explores, from the perspective of patent and drug development law, the possibility for so-called generic biologics and the ramifications and strategic concerns for innovators raised by that possibility.

Will We Be Seeing Generic Biologics Soon?

Datamonitor, a market analysis company, has reported that more than $10 billion worth of biopharmaceuticals are scheduled to go off-patent by the end of 2006 (1). Accordingly, the potential market for generic biologics (in contrast with generic pharmaceuticals) has been drawing increased attention from generic and branded drug developers, regulatory agencies, advocacy groups, and lawmakers.

Currently, generic biologics cannot be marketed in the United States. The Drug, Price Competition and Patent Restoration Act of 1984, commonly known as the “Hatch-Waxman Act,” and its corresponding regulations provide a complex set of rules that govern the approval and market-entry of generic drugs (2). However, the Hatch-Waxman Act’s Abbreviated New Drug Application (ANDA) provisions specifically exclude biologics. The Hatch-Waxman Act represents a compromise between the interests of lowering drug costs (achieved by expediting regulatory approval of generic copies of off-patent drugs already approved for marketing by the FDA) and encouraging development of novel drugs (achieved by providing limited opportunities to extend the terms of patents covering pioneer drugs).

Congress likely did not include biologics within the scope of the Hatch-Waxman Act’s ANDA provisions because only a few biotechnology-derived drugs existed when the act was enacted in 1984. Perhaps Congress also appreciated the difficulty in verifying bioequivalence in biologically derived drugs given the extant technology. In any event, recent socioeconomic and political changes, along with continuous technological improvements in the ability to produce and test biologically derived drugs, have significantly increased the likelihood that a regulatory framework permitting generic biologics in the US marketplace will emerge.
AN EXISTING PATH TO GENERIC BIOLOGICS?
Even though the FDA has made clear that it will not approve generic biopharmaceuticals under existing ANDA provisions, the Hatch-Waxman Act may provide another means for obtaining such approval. FDA’s Center for Drug Evaluation and Research (CDER) has indicated that the ANDA regulatory scheme does not allow the FDA to obtain enough evidence to approve a generic biopharmaceutical, due in part to CDER’s inability to request additional preclinical or clinical testing under an ANDA. Nevertheless, proponents of generic biopharmaceuticals have asserted that section 505(b)(2) of the Hatch-Waxman Act provides a new drug application pathway that may serve as an ANDA-like approach to approval of generic versions of complex biologics originally approved under biologic license applications (BLAs).

Indeed, in October 1999, the FDA announced that the section 505(b)(2) pathway may serve as a way to obtain regulatory approval of a generic version of certain biological products originally approved under a new drug application (NDA) (3). A section 505(b)(2) application would permit an applicant to obtain approval of an NDA based on the FDA’s earlier findings of safety and efficacy from a previously approved NDA and thus would not require an applicant to obtain a right of reference from the original applicants. The section 505(b)(2) applicant must also provide any additional clinical data needed to demonstrate that differences between the original drug and its copycat have not changed its safety and effectiveness (4).

Moreover, just like an ANDA applicant, a section 505(b)(2) applicant must include appropriate patent certifications and explain the basis upon which it believes that it does not infringe any valid claim of a so-called “Orange Book” listed patent (5). Under 35 USC § 271(e)(2), the holder of the original NDA, and putative patentee, could then bring suit against the later applicant and obtain a 30-month stay of the section 505(b)(2) approval. Products marketed under approved section 505(b)(2) applications, like ANDA-based products, may receive an “AB” substitutability rating in the Orange Book if the product has the same active ingredient(s), dosage form, strength, and bioequivalence.

QUESTIONS REMAIN
Although section 505(b)(2) appears to provide a potential pathway for the approval of generic biologics, several questions surrounding the FDA’s regulatory structure and authority make it unclear whether the agency would approve generic biologics by this route. A recent citizen petition, filed on behalf of Pfizer Inc. and Pharmacia, has requested that the FDA cease approving section 505(b)(2) approvals and asserts that the section does not allow the agency to rely on or use an innovator’s proprietary data to approve NDAs. The still-pending citizen’s petition argues that any such use would constitute a taking in violation of the Fifth Amendment to the US Constitution. Moreover, because it allows reliance on safety and effectiveness results of original NDAs approved by CDER, section 505(b)(2) may not apply to the vast majority of currently marketed biologics, which obtained approval from distinct applications before the Center for Biologics Evaluation and Research (CBER).

Nonetheless, the fact that most biologics were approved by CBER under the Public Health Service Act might not preclude the use of section 505(b)(2) to approve generic versions of them. Just this year, the FDA has shifted oversight of most biologics from CBER to CDER. The shift is extensive and includes monoclonal antibodies, cytokines, growth factors, enzymes, interferons, proteins intended for therapeutic use that are extracted from animals or microorganisms, and therapeutic immunotherapies. CBER will continue to regulate gene and cellular therapies, blood products, vaccines, antitoxins, and allergens and those antibodies, cytokines, and proteins used solely in manufacturing processes or as reagents. The review of various biotechnology-derived NDAs and BLAs by CDER may provide an avenue for the application of section 505(b)(2) to generic biologics relying on the original biologics’ applications.

CAN BIOEQUIVALENCE BE DEMONSTRATED ANALYTICALLY?
At the center of the conflict over potential FDA regulatory pathways for approval of biologic generics is conflicting views regarding the feasibility of determining bioequivalence without requiring extensive clinical testing. The use of chemical specifications as criteria for determining bioequivalence has worked well for relatively small molecules.

Most small-molecule therapeutics, those smaller than 1,500 D for example, can be based solely on a specified and controlled chemical structure. Such a structure is generally determined readily by nuclear magnetic resonance, mass spectrometry, infrared spectrometry, X-ray crystallography, or other well-known physical methods.

Biologics, on the other hand, typically contain active macromolecules and therefore exhibit far more complexity and...
generics manufacturers to successfully reverse-engineer the process.

**The FDA Has the Authority**

Recent FDA guidance and court decisions indicate that the FDA does have the authority and flexibility to allow approval of generic biologics by means of establishing bioequivalence. For example, in the case of *Serono Laboratories, Inc. v. Shalala*, the United States Court of Appeals for the District of Columbia Circuit ruled that the FDA has the authority to make scientific judgments regarding what constitutes “sameness” in the context of comparing the active ingredients in two drug products. Indeed, FDA-approved biologics from different manufacturers are already on the market. Significantly, an FDA guidance document on demonstrating comparability permits product-based comparison of biologically derived drugs. It states, in part:

> [W]hen a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study, it may not be necessary for the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent.

Thus, the FDA has shifted its focus from manufacturing processes to the safety, purity, and potency of the resulting product. Because the characteristics of the final biologic product may be easier to determine and control than the similarity of the production processes, the FDA may find that establishing bioequivalence of generic biologics is possible. Thus, the FDA and the courts may well conclude that the FDA has the authority — and the ability — to establish standards of bioequivalence in allowing approval of generic biologics.

**Congress May Change the Rules**

In addition to the possible use of existing provisions to approve generic biologics, the FDA may soon have new options. Lawmakers are currently crafting and gathering support for bills that provide an explicit means for FDA approval of generic biologics. Among such lawmakers are Senator Orin Hatch (R-Utah), the named Senate sponsor of the Hatch-Waxman Act, and Senator John Rockefeller (D-West Virginia). Although the specifics of Senator Hatch’s bill have not yet been publicly revealed, Senator Rockefeller’s has been introduced and contains express provisions for FDA regulation of generic biologics. Support from public interest groups and industry organizations, such as the Generic Pharmaceutical Association (GphA) — an organization that represents about 140 members of the generic drug industry — may well increase the likelihood that Senator Rockefeller’s proposed law, or one like it, will receive significant attention in the coming years.

Although the regulatory and scientific issues concerning generic biologics continue to be hotly debated, it is clear that Congress and the FDA are likely to address the many issues raised by their possibility as valuable biologics patents expire.

**In the Meantime, How Can You Best Use Your Patents?**

Even if generic biologics are never recognized by statutes or the FDA, existing law provides important guidance for biopharmaceutical innovators and manufacturers. Specifically, patent law provides a defense for activities that would otherwise constitute patent infringement if those activities are “solely for uses reasonably related to the development and submission of information” to the FDA (8). In recent years, the lower courts had interpreted this rather cumbersome phrase to provide a safe harbor to developers of any FDA-regulated drug or medical device, effectively creating a shield that spanned from relatively early-stage development...
through (and even perhaps beyond) FDA approval. However, in June 2003, the court of appeals that handles patent matters disagreed. In *Integra Lifesciences v. Merck* (9), the court of appeals held that the safe harbor does not protect the development, screening and identification of new drugs. Rather, it protects only activities that “directly produce activities for the FDA” and other, closely related conduct. Accordingly, companies that engage in domestic research and development efforts, as well as those that hope to develop and enforce valuable patents, should pay special attention to this important case and how it is implemented by the lower courts.

In a related vein, patent law provides an opportunity to extend the term of certain patents that claim an active ingredient of an FDA-approved “new drug, antibiotic drug, or human biological product” (10). Thus even though this patent term extension provision and the ANDA provision of the Hatch-Waxman Act were generally seen as balancing competing interests, this extension provision pertains to human biological products, whereas the ANDA provisions, as explained above, currently do not. Moreover, because the rights conferred during the extension are essentially limited to the approved drug product, competitors will have opportunities to work around the patent during the term extension that do not exist during the original patent term. Furthermore, only one patent may be extended for any given FDA approval, and only specific patents — ones that “claim” the drug — may be extended. Awareness of the limited rights during term extensions, as well as the criteria for selecting the patent to extend, are each essential to developing a strong biologics patent portfolio — and to attacking such a portfolio.

Of course, if generic biologics do become a reality, it is likely that the statutes and regulations will seek to strike a balance between innovators’ rights and generic market entry, as in the Hatch-Waxman Act. Thus, any relevant legislation may well resemble, or simply borrow from, the Hatch-Waxman Act. In that case, lessons learned through the years of enforcement and administration of the Hatch-Waxman Act in the context of pharmaceuticals will be invaluable when similar legislation extends to biologics. For example, case law shows that certain patent-based “life-cycle management” techniques have proven successful for pharmaceutical innovators confronting potential generic competition. On the other hand, the government has considered other more aggressive techniques to be violations of the federal antitrust laws and has brought appropriate legal action against innovators that have employed these techniques. Full awareness of the distinctions between appropriate and unlawful conduct in this context will be essential to the success of innovators and their generic competitors in the field of biologics.

The possibility that Congress and the FDA will permit generic biologics is real, even though the administrative hurdles that must first be cleared are daunting. Forward-looking companies should begin to craft their patent strategies now, so that they will be properly positioned when and if the law changes.

**REFERENCES**

4. See, for example, *Procedure for Submission of an Application Requesting Investigations for Approval of a New Indication for, or Other Change from, a Listed Drug. US Code, Section 21 Title 314.54, 2003.*
5. *Approved Drug Products with Therapeutic Equivalence Evaluations.* The FDA’s listing of approved drug products is commonly referred to as the “Orange Book” and is accessible in electronic form at www.fda.gov.cder/ch/default.htm.

**Corresponding author Joseph M. Reisman** is a partner in and Arman H. Nadershahi is associated with the law firm of Knobbe, Martens, Olsen & Bear, LLP, 550 West C Street, San Diego, CA 92101. The views expressed herein are not intended to constitute legal advice, are solely those of the authors, and do not necessarily represent the views of Knobbe, Martens, Olsen & Bear, LLP or any client of Knobbe, Martens, Olsen & Bear, LLP.