PHARMACEUTICAL LAW

IS "SIMILAR" SAFE ENOUGH? A REVIEW OF THE TECHNICAL AND LEGAL ISSUES DELAYING GENERIC BIOPHARMACEUTICALS

*By M. Veronica Mullally**

In 2005, sales of biopharmaceuticals rose 17.2% to $32.8 billion and it is predicted that by 2010 the market for biopharmaceuticals will be worth over $106 billion according to independent market analyst Datamonitor. Accordingly, it is not surprising that, with patent coverage set to expire on biopharmaceuticals worth tens of billions of dollars during the next few years, there is growing pressure for access to generic biopharmaceuticals (also called biogenerics, follow-on biologics, biosimilars and generic biologics). Because they are typically complex protein molecules produced by natural processes in living cells, when the same biopharmaceutical product is made by different manufacturers the products of their different cell lines are not identical. This makes the bioequivalency determination for a generic biopharmaceutical extremely problematic and is the main reason that there is currently no regulatory framework for the approval of generic biopharmaceuticals in the U.S. As a result, brand name biopharmaceuticals are largely protected from the generic competition common to traditional small molecule drugs.

Although, generic manufacturers and even state governors have pressed the FDA to approve generic biopharmaceuticals, the FDA has remained adamant that existing provisions of the Hatch-Waxman Act (Hatch-Waxman) cover only small molecule drugs and the few proteins that have been approved as drugs under Section 505(b)(1) of the Food Drug and Cosmetic Act (FDACA). These provisions are not applicable to the more complex biopharmaceuticals licensed under Section 351(i) of the Public Health Service Act (PHSA). Meanwhile, the European Medical Agency (EMEA) has issued guidelines for approval of biosimilar drugs and has already approved generic versions of recombinant human growth hormone under those guidelines. In September 2006, a bill addressing generic biopharmaceuticals, the Access to Life-Saving Medicine Act, was introduced in both the House and the Senate and it seems that the time has finally come for Congress to address whether a new legislative scheme is necessary and/or appropriate to provide for generic biopharmaceutical

* *M. Veronica Mullally, is a partner in the New York office of Orrick, Herrington & Sutcliffe LLP. Ms. Mullally is a patent lawyer specializing in patent litigation, due diligence and strategic counseling in the life sciences. She has handled multiple cases involving recombinant DNA technology and also has extensive Hatch-Waxman experience. Before attending law school, Ms. Mullally was a research scientist at Celltech (U.K.) where she helped develop some of the first diagnostic uses of monoclonal antibodies.*

approval. The pending legislation is discussed below along with some of the technical issues that must be addressed before a workable regulatory scheme for generic biopharmaceuticals can be established and some of the practical hurdles facing would-be manufacturers of generic biopharmaceuticals in the U.S.

Biopharmaceuticals are more complex than traditional small molecule drugs.

Biopharmaceuticals are "biologics" and unlike small molecule drugs which can be made in a laboratory, they are produced in living cells. Biologics are typically proteins such as hormones or monoclonal antibodies and are regulated by the FDA through the Biologic License Application (BLA) provisions of the PHSA. However, a small number of biopharmaceutical proteins have been approved by the FDA as "drugs" under Section 505(b)(1) of the FDACA, including: recombinant growth hormone, recombinant glucagon, recombinant calcitonin, and recombinant hyaluronidase. The FDA distinguishes these biopharmaceuticals from the more complex biologics (*i.e.* those that have high molecular weight, multiple sub-unit proteins and post-translational modifications) and those that cannot be adequately characterized and/or have unknown active ingredients or mechanisms of action. It is because of their inherently complex structures and methods of production that these more complex biopharmaceuticals are regulated under the PHSA via BLAs. However, this disparate approach to the approval of biopharmaceuticals by the FDA has led to great confusion with regard to attempts to obtain approval of generic versions of biopharmaceuticals and it is compounded by the guidelines issued by the FDA, in 2001, regarding 505(b)(2) Paper NDA's. Those guidelines state that "[n]aturally derived or recombinant active ingredients" may be suitable for a 505(b)(2) application and that "clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a *listed drug*." (*emphasis added*) The confusion arises because most biopharmaceuticals are approved under the PHSA and, thus, cannot be a "listed drug" that a generic manufacturer can reference in a 505(b)(2) application under Hatch-Waxman.

Omnitrope – the first generic biopharmaceutical approved in the U.S.

The first U.S. generic biopharmaceutical, Omnitrope (recombinant human growth hormone "hGH"), was approved in May 2006, but only after the FDA had been sued and was ordered by the court to act on Sandoz's 505(b)(2) application. Under the Hatch-Waxman provisions, a generic manufacturer can rely on clinical trials completed for the brand name drug because the active ingredient in the generic is identical to that in the reference listed drug. Sandoz brought a 505(b)(2) application under the Hatch-Waxman provisions for approval of its generic hGH product because the reference product, Pfizer's Genotropin, was ap-

proved as a "drug" under 505(b)(1) via an NDA. Pfizer argued against the approval on the basis that generic versions of biopharmaceuticals are never identical to the comparator product and Sandoz should not have been allowed to reference public data on Genotropin in its NDA. Pfizer also argued that Sandoz's drug should not be considered bioequivalent without a full clinical trial because of the safety risks associated with even small changes in the biopharmaceutical product. This argument has also been used as a general reason why the FDA should not approve "generic biologics" without additional statutory authority. Indeed, the FDA has been caught in the crossfire between branded drug and biotech companies who want to block generic competition and generic manufacturers who want to get into the lucrative biopharmaceutical market without having to conduct all the costly clinical testing conducted by the innovators. For their part, innovator companies argue that the science is not advanced enough to allow generics to bypass clinical trials because biologic molecules are so much harder to characterize and thus it is harder to prove equivalence than with a small molecule. Generic manufacturers, on the other hand, argue that there is no reason to delay consumer access to affordable medicines when sound science supports the approval of generic biopharmaceuticals via an abbreviated less costly route. Against this background, the FDA found approval of Sandoz's product to be "scientifically justified" because hGH is not glycosylated and has characteristics that facilitate comparison of the two products. But, even after it had approved Omnitrope, the FDA repeatedly stated that the approval did not herald the approval of other generic biopharmaceuticals and again acknowledged that there are no approval provisions for generic versions of more complicated biopharmaceuticals licensed under the PHSA.

Generic biologics in Europe and other markets

Europe is further ahead than the U.S. in providing a route to approval for generic biopharmaceuticals. The EU passed legislation in 2003 that establishes a regulatory pathway for abbreviated approval of follow-on biologics and has continued to amend it. Although the European Medicines Agency (EMEA) has stated that the standard "generic approach for gaining marketing approval is not scientifically appropriate for these products," in 2005, it released draft guidance documents containing requirements for the approval of biosimilar versions of four biologic products. The agency proposed comparability studies needed to prove the similar nature of the "new similar biological medicine product" and also stated that preclinical and clinical data would be required to establish safety and efficacy. Since then, at least two biosimilar growth hormones have obtained European approval under this abbreviated approval program. However, the recent rejection of a biosimilar application by BioPartners GmbH for recombinant interferon alpha-2a (Alpheon), essentially a copy of Hoffman-La Roche's Roferon-A, highlights some of the difficulties that arise with abbreviated applications for more complex

biopharmaceuticals and shows that obtaining biosimilar approval is not going to be as simple as some companies expect.

The rest of the world is not waiting for U.S. legislators and the FDA to decide on an approach to generic biopharmaceuticals. While they cannot gain entry to the most lucrative U.S. and European markets, some generic companies are targeting countries with lower regulatory barriers and less stringent intellectual property protections. Dragon Pharmaceuticals, a Canadian biotech company based in Vancouver is one of several companies selling generic EPO in unregulated markets. Dragon manufacturers EPO in China and sells it into 8 countries: India, Egypt, Trinidad-Tobago, Dominican Republic, Brazil, Peru, Ecuador and Kosovo. Companies who are actively selling biogenerics into unregulated markets may have the advantage over those who have decided to wait for regulatory access to the more lucrative Western markets because they are already earning income on their biogenerics investment while refining their capabilities well in advance of entry into the U.S. and European markets.

How safe is similar?

Because biopharmaceuticals are produced by different manufacturers in different cells lines by different processes, the products, albeit similar, are never identical. So, the central problem facing regulatory agencies on the issue of generic biopharmaceuticals has been how best to determine bioequivalency when the generic version is only similar to the reference drug. Experience shows that biopharmaceuticals are susceptible to different safety concerns to small molecule drugs. Nature Biotechnology recently reported that Dutch scientists had discovered that aggregates in the formulation of recombinant human erythropoietin (EPO) sold as Eprex in Europe, were responsible for an immunogenic reaction that triggered severe side effects in patients a few years ago. According to that report, the manufacturer of Eprex, Ortho Biotech, in response to a request from the EMEA, had replaced its usual stabilizer Human Serum Albumin with a non-human source stabilizer, sorbital, to reduce risk of contamination by HIV or BSE-causing prions. But, the sorbitol caused formation of micelles that clustered with the EPO and triggered an immunogenic response. The antibodies formed not only undermined the Eprex but also attacked any naturally occurring EPO leaving the patients with red cell aplasia and requiring frequent blood transfusions for survival. As a result, the multiple companies currently seeking approval for generic EPO in Europe will likely need to present clinical trial evidence on immunogenicity.

The risk is certainly not limited to EPO. Almost all protein biopharmaceuticals have the potential to induce immunogenic reactions which could be triggered by differences in the amino acid sequence or glycosylation pattern or by impurities or a change in the formulation as in the Eprex case. Obviously, adding clinical trials into the generic approval

process increases development costs and, depending on how extensive the clinical trials are required to be, there may be a reduced incentive for generic manufacturers getting into the market. For these reasons, we may never see price reductions for biopharmaceuticals equivalent to those associated with small molecule generic drugs.

The proposed legislation.

Over twenty years ago, when Congress developed the Hatch-Waxman provisions for approval of small molecule generic drugs, biopharmaceuticals were barely on the horizon and because issues related to bioequivalence were so difficult, lawmakers chose to ignore generic biologics. Now, twenty-two years later, over 300 biopharmaceuticals have been approved. Recognizing that they are among the most expensive of drugs and with numerous biopharmaceuticals coming off patent, lawmakers have drafted legislation that attempts to provide an abbreviated route to approval for generic versions of biopharmaceuticals. Although it is unlikely to be enacted exactly as it stands, for the first time there is credible legislation up for debate. The Access to Life-Saving Medicine Act introduced into the Senate by Senators Schumer, Clinton, Leahy and Stabenow, seeks to amend the PHSA and the patent laws at 35 U.S.C. §271(e).

Under the proposed amendments, the generic application would be a "comparable biological product application," where "comparable" is defined by "the absence of clinically meaningful differences between the comparable biological product and the reference product in terms of safety, purity, and potency. . .." The comparability determination would be based on "data derived from chemical, physical and biological assays. . .and. . .any necessary clinical study or studies sufficient to confirm safety, purity and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used." The proposed amendments expressly provide that glycosylated proteins with differences in structure due solely to post-translational events, infidelity of transcription or translation or minor differences in amino acid sequences may be considered comparable, notwithstanding minor differences in heterogeneity profile, impurities, or degradation products. Presumably, the FDA would decide what "clinically meaningful differences" are and to what extent establishing their absence requires clinical trials.

While the proposed amendments provide for an exclusivity period for the first generic applicant and specifically excludes authorized generics during that period, there is no provision for a stay of approval pending any patent litigation as there is in the Hatch-Waxman scheme. Neither is there any suggestion that the BLA holder must list relevant patents. Instead, under the proposed legislation the generic manufacturer must directly ask the innovator to provide information on patents that cover the reference product, any method of use, any component of the product and any method or process of manufacturing it. After receiving the patent information, the generic applicant may send a notice letter

to the innovator identifying which patents it believes are invalid, not infringed or unenforceable and which jurisdictions it consents to be sued in. The innovator then has forty-five days to bring an infringement suit, but only in one of the jurisdictions identified by the generic applicant. If relevant patents are not disclosed to the generic applicant in a timely fashion or if a suit is not brought within the forty-five days, the BLA-holder can not later enforce the relevant patents against the generic manufacturer. The proposed amendments also provide that a generic applicant may ask the FDA to make a determination of "interchangeability." Upon a determination that the generic is interchangeable with the reference product, interchangeability may be stated on the biogeneric's label. The version of the bill introduced into the House would also amend the Tax Code to provide a fifty percent credit against taxes for qualified clinical testing used to demonstrate comparability and defines such testing.

Additional factors that may limit incentive for generic manufacturers.

In addition to the costs of development and clinical work that is likely to be required for approval, the cost of manufacturing biologics is much higher than for small molecule drugs. Consequently, the price reductions for generic biologics are unlikely to mirror the up to eighty percent that has been seen with generic small molecule drugs and one has to wonder whether doctors and patients will switch to a generic which is only ten to twenty percent less expensive than the innovator drug. But, perhaps the biggest concern for potential biogeneric manufacturers is the fact that many biopharmaceutical manufacturers are already taking steps to extend their products' lifecycle by developing second generation products. Some have contracted for Direct Molecule Evolution (DME) studies on their drugs as a method of optimizing the protein and extending the product's life cycle. DME is a technique that mimics natural evolution to optimize protein candidates. For example minor alterations of the amino acid sequence can change the protein's glycosylation pattern and thereby change the pharmacokinetics and length of time it remains in the circulation. If patients are already switched to a second generation extended release formula that means a weekly injection instead of a daily injection by the time a generic is approved, they are unlikely to switch back to the first generation product even if the generic is cheaper.

What's in a name?

Another issue currently being raised about generic pharmaceuticals and the fact they are similar but not identical to the branded drugs they copy, is the need for an appropriate nomenclature for generic biopharmaceuticals. The major European and U.S. pharmaceutical and biotechnology trade associations recently banded together to support a proposal that WHO adopt a policy of granting unique International Non-

proprietary Names to each biopharmaceutical product from each company. Innovator industry groups are advocating various naming schemes for generic biologics which would tie them to their original manufacturer ostensibly to make it possible to trace the cause of any adverse health events. The claim is that conventional nomenclature systems do not take into account the complexity and unique issues associated with biopharmaceuticals and their manufacturing processes. But generic makers oppose the idea of generics having different common names to the brand-name biopharmaceuticals they copy because it would prevent the generics from being substituted for the branded drug. They argue that the real aim of such a labeling scheme is not for safety reasons but rather to protect the innovators' market share.

THE PATH TO BIOGENERICS IN THE U.S. MAY NOT BE SMOOTH, BUT IT WILL LIKELY BE PAVED.

Regardless of the many hurdles that exist along the route to approving generic biopharmaceuticals in the U.S., generic manufacturers will likely get there. Evidencing their confidence in that outcome, many companies are aggressively positioning themselves. For example, Teva Pharmaceutical Industries Ltd has bought plants in Mexico and Lithuania to make biogenerics and, generic drug makers are partnering with biotech companies to get access to the technology and know how necessary for manufacturing biologics.

Controlling health care costs is likely to be a top priority for the new Democratic majority in Congress and one way to achieve that goal is to provide access to cheaper generic versions of biopharmaceuticals. Therefore, legislation to provide for generic biopharmaceuticals is more likely to be enacted—perhaps sooner than previously expected. While the pending legislation provides an immediate vehicle for debate, it is unlikely to be enacted without significant modification. Nevertheless, it now seems inevitable that a regulatory scheme providing for approval of biogenerics in the U.S. will emerge within the next few years. As Representative Waxman stated, "The important thing will be to make sure that the reforms that will inevitably come are thoughtful, careful and strike the right balance between encouraging innovation and encouraging competition."