Legal Backgrounder

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REGULATORY PATHWAY FOR "BIOSIMILAR" PRODUCTS DEBATED

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Patents on a number of breakthrough biological treatments are nearing expiration. Competitors hang in the wings. The degree to which regulatory approval is sought for additional products is likely to depend on an intense legislative debate as part of Prescription Drug User Fee legislation. The following discussion is intended to serve as a primer concerning the FDA review of new biological products of the same type as products already approved.

What is a Biologic? A biologic is a product that is derived from a living organism and used in the prevention, treatment, or cure of a disease. 42 U.S.C. § 263a. Biologics include vaccines, hormones, human growth factors, enzymes, clotting and anti-clotting factors, and recombinant protein products. While drugs are also products that are intended for the diagnosis, prevention, treatment, or cure of a disease, 21 U.S.C. § 321(g)(1)(B), § 201(g)(1)(B) FDCA, drugs are typically derived from chemical compounds. Drugs are also regulated exclusively under the Food, Drug, and Cosmetic Act (FDCA). The Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) has jurisdiction over drug approval and marketing. The vast majority of biologics, however, are regulated under the Public Health Service Act (PHSA). CDER also has jurisdiction over most biologics approval and marketing.[1]

Relative Importance to Health Care Market. Biologics represent an $18 billion industry in the United States and $56 billion worldwide. Ben Hirschler, *EU Tipped to Get Generic Biologics This Year*, Reuters Jan. 16, 2006. Currently encompassing about 10 percent of the pharmaceutical market, biologics are growing at twice the rate of conventional prescription drugs. Henry Grabowski, Iain Cockburn & Genia Long, *The Market For Generic Biologics: How Will It Evolve?*, 25 HEALTH AFFAIRS 1291, 1294-5 (2006). They can, therefore, be expected to represent an increasing share of the pharmaceutical market. In addition, biologics are more expensive than conventional drugs, ranging in cost from several thousand dollars per year to more than $200,000. Cyril T. Zaneski, *Modern-Day Miracle: New Biodrugs are Growing in Use and Cost*, BALT. SUN, Mar. 24, 2004.

[1]The FDA Center for Biologics Evaluation and Research (CBER) retains jurisdiction to review applications for blood-based biologics products.

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Biologics are likely to drive health care costs steadily higher. Concerns, therefore, exist about their potential financial impact and continued patient access to lifesaving therapies. Were these products conventional drugs, then manufacturers could enter the market with FDA-approved generic versions that would cost significantly less than the brand equivalents. However, because the vast majority of biologics are regulated under the PHSA, and there presently are no provisions under the PHSA for the commercial marketing of generic biologics, these products are not widely available to the public.

Complexity of Biologic Products. Biologics are typically large protein molecules derived from living cells and manufactured through DNA or RNA synthesis. Drugs, by contrast, are typically small molecules derived from chemical synthesis. Drugs also typically have well-defined structures. Biologics tend to be a mixture of heterogeneous proteins and impurities, each of which may contribute to the product's biological activity, efficacy, and safety in ways that may be only partly understood, controlled, and reproduced. Thus, a given biologic is not generally interchangeable with another. In addition, small changes in the manufacturing process could produce a dramatically different product. Consequently, it is crucial that biologic manufacturing processes have extensively validated process controls, well-established reference standards at all stages, and definitive release specifications to ensure product safety and effectiveness.

A generic biologic produced by another manufacturer using a distinct manufacturing process could likely produce a product different than intended. Many in industry, therefore, believe that extensive safety and efficacy testing would be required in order to market these products. Further, many believe that due to the complexity of the development and testing of biologics, any generic versions would likely result in more modest savings than generic versions of conventional drugs. Others believe that even a price reduction of at least 20 percent could result in significant savings to consumers.

Legal Pathway for Commercial Marketing of Generic Biologics under FDCA. FDA contends that a regulatory route to approve a generic biologic exists under section 505(b)(2) of the FDCA. Still, this pathway would not apply to products approved by a biologics license application (BLA) under the Public Health Service Act (§ 351). BLA products, in FDA's view, would require new legislation amending the PHSA to permit approval of a generic or biosimilar biologic.

Under § 505(b)(2) of the FDCA, FDA may rely for approval of a new drug application (NDA) on data not developed by the applicant. Some or all of the additional clinical information could be provided by the literature or by references to past FDA findings of safety and effectiveness for approved drugs. According to FDA, the applicant can rely on established conclusions about the approved drug to the extent these conclusions are applicable to the proposed product. Notably, FDA contends that the applicant must supply data to support any differences between the two products. Precisely what additional data will be necessary is generally the subject of discussion between the sponsor and FDA during the product development process, and the amount and quality of requested data is generally within the discretion of FDA. By permitting appropriate reliance on what is already known about an approved product, FDA states that industry is allowed to focus upon innovative product development.

FDA Approval of Omnitrope™. In April 2006, the U.S. District Court for the District of Columbia decided the case *Sandoz v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006). In that case, FDA was ordered to act on a 505(b)(2) new drug approval (NDA) application filed by Sandoz for Omnitrope™ (somatotropin [rDNA origin]), a generic version of Pfizer's Genotropin, synthetic human growth hormone. In May 2006, FDA ultimately approved the application interpreting 505(b)(2) to use a "sufficiently similar" standard as opposed to the generic drug "bioequivalence" standard required by 505(j). Notably, FDA stated that Omnitrope's approval did not create a direct precedent for generic versions of other products.

In addition, FDA explicitly stated that the 505(b)(2) approval pathway cannot be utilized for products originally licensed under section 351 of the PHSA. FDA further emphasized that the relative lack of complexity of the hormone, the availability of current analytical technology, and available compendial standards greatly simplified agency review. These distinguishing characteristics, in FDA's view, made it unnecessary for FDA to rely on proprietary data from the existing applications of other human growth hormone manufacturers. *See* FDA, Omnitrope Questions and Answers, at: http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm.

As such, FDA has provided some informal guidance regarding the likelihood of approval of future generic biologic applications under 505(b)(2). That is, a generic biologic most likely will be approved under the 505(b)(2) pathway when: (1) it is a product that has traditionally been regulated under the FDCA as an NDA and not under the PHSA as a BLA; (2) it shares other key characteristics with reference biologics, in particular, their proposed strengths, indications, route of administration, and conditions of use; (3) FDA's prior finding of safety and effectiveness for the reference product provides some, but not necessarily all, support for the proposed generic's approval; and (4) data demonstrate that the proposed product, to the extent that it differs from the listed product referenced in the application, is safe and effective. For example, any impurities found in the proposed product that were not present in the reference product should be adequately characterized by non-clinical and clinical studies and should be found not to have a negative impact on safety or effectiveness.

Additional Issues in the Debate over the Marketing of Generic Biologics. Many in industry believe that FDA does not have the authority to approve a proposed product under the 505(b)(2) pathway by relying on information contained in other product applications, especially when that information is alleged to be trade secret and confidential commercial information. This is especially important with respect to biologics that frequently use proprietary manufacturing techniques. FDA refutes this position by stating that the plain language of 505(b)(2) permits applicants to rely on studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use." FDA claims that the FDCA does not limit the sources of the studies, on which 505(b)(2) applicants may rely, to published literature or other publicly available studies – even though Congress could easily have added such a limitation.

Immunogenicity. Many in industry also contend that immunogenicity is a major concern in the manufacturing and commercial marketing of generic biologics. Immunogenicity is essentially an allergic response that can originate in the manufacturing process and from intrinsic properties of the biologic. Timothy Coan and Ron Ellis, *Generic Biologics: The Next Frontier*, ABN-AMRO Incorporated (June 2001). It can result from a single amino acid change. Depending on the degree of immunogenicity, the efficacy of the biologic can be dramatically altered. Still, others in industry argue that immunogenicity is a concern with any product and not just generic biologics. *See* GPhA white paper: *Biopharmaceuticals (Generic Protein Products): Science and Considerations for an Abbreviated Approval Pathway* at: http://www.gphaonline.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=1573.

European Pathway for Generic Biologics. The European Union (EU) recently laid out a regulatory framework for what a generic manufacturer is required to provide in order to market a generic biologic (known within the EU as a similar biological medical product). Specifically, the regulatory body that approves the marketing of medicines within the EU, the European Agency for the Evaluation of Medicinal Products (EMEA), acknowledges that bioequivalence demonstrations used for existing generic drug products would not be appropriate in the biological sector. Rather, the key to marketing a generic biologic within the EU turns on whether a manufacturer is able to demonstrate "comparability" of its proposed generic biologic to the reference biologic product. To ensure that biologics remain affordable and accessible in the United States, many believe that it is imperative that federal policymakers consider the EU framework and develop a way for generic biologics to come to market.

Patent and Marketing Exclusivity Issues. The manufacturing process for biologics can be critical to the product's authenticity—the growth of an organic component rather than the synthesis of chemical compounds can create certain challenges to ensuring that the same product is reproduced. Consequently, biologics tend to have multiple patents, ranging from a patent on a particular cell line to a patent for the manufacturing process. Alison Langley, *International Business; Engineered Drugs Open New Issue Of Regulation As Patents Expire*, N.Y. TIMES, Aug. 9, 2003. As such, for many in the biotech industry, "the process is the product. Stephan Herrera, Biogenerics Standoff, 22 Nat. Biotech. 1343-46 (2004), available at: www.nature.com/news/2004/041108/pf/nbt1104-1343_pf.html.

However, FDA believes that some biologics are not necessarily defined by their manufacturing processes. State-of-the-art analytical techniques can determine that two products are sufficiently similar even though they may be produced through different processes. Thus, a generic manufacturer might be able to design around an innovator's patents and acquire regulatory approval of its product. In this regard, the possible loss of market

protection presents a concern to many innovators. Many manufacturing techniques are also public through published literature.

Regardless of whether innovator products are defined by their manufacturing processes, a regulatory pathway will need to be delineated for resolution of patent challenges. The concern is that to the extent that a generic biologic is not required to be the same as an innovator product, a generic manufacturer might be able to avoid innovator patents and still produce a sufficiently similar product for the purposes of regulatory approval. Congressional legislation and the FDA will also need to take into consideration the grandfathering of already approved generic biologics, to the extent that this approval pathway differs from the final statutory and regulatory processes created.

Access to Life-Saving Medicine Act. In the closing days of the 109th Congress (September 2006), legislation was introduced to create a regulatory pathway for drugs deemed generic or biosimilar to reference biologic products. The Access to Life-Saving Medicine Act (S. 4016 and H.R. 6257) amends § 351 of the PHSA to create express regulatory authority for FDA to approve applications for biological products that are "comparable" to previously approved (reference) biological products. A comparable biological product application need not show safety and efficacy, but that there are no clinically meaningful differences between the two products. The application must also show that the new product shares the "principal molecular structural features" of the reference product and the same mechanism of action, if known.

FDA is granted the discretion on a case-by-case basis to determine what studies are necessary to establish comparability. An applicant may elect to establish "interchangeability" in addition to comparability that will accord the ability for providers to substitute one drug for another and obtain a period of exclusive marketing during which no other interchangeable version of the product may be approved. Certain patent and marketing exclusivity issues (as noted above), however, remain unresolved.

Conclusion. New legislation from Congress most likely will be required to provide for the approval of generic biologics since existing authority under § 505 does not apply to § 351 BLA products. However, because of the controversy over biologics regulated under the FDCA, FDA could also clarify elements of its approval process via guidance documents, or notice and comment rulemaking (not likely given the time-consuming process). In light of the controversial nature of the generic biologics debate, FDA has limited its role to review of products approved initially using NDAs and not BLAs. It appears content to provide technical guidance to congressional legislative drafters who will likely create a Hatch-Waxman type system for biologics. The system will likely acknowledge the need to discount sameness for use of a sufficiently similar standard, and the need to evaluate manufacturing processes as part of any generic biologic application.

Consideration of the Prescription Drug User Fee Act reauthorization bill in 2007 is a major engine pushing the current dialogue. Brand name pharmaceutical manufacturers stress that generic biologics will never be the "same" as the already approved products in the generic sense. While the organic nature of biologics likely prevents the manufacture of an identical product by another pharmaceutical company, because even the approved product varies lot-to-lot, the technology exists to produce similar products. Indeed, as noted above, FDA believes that a similar comparability standard, and not a "sameness" or interchangeability standard, should be applied to generic biologics. This standard would include utilizing a battery of tests to determine comparability, safety, and effectiveness.

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