FOLLOW-ON BIOLOGICS IS AN ABBREVIATED APPROVAL ON THE HORIZON?

While legislation governing biologics is currently being debated throughout the world, biopharma and biotech companies have to take greater care to protect their intellectual property

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INTRODUCTION

Generic pharma industry is a multi-billion dollar industry, wherein the United States represents a large market, particularly for Indian companies. Biologics or biopharmaceuticals have been around for a few decades now, and the first round of these products is about to lose patent protection. However, while the Hatch Waxman Act allows expedited approval of a drug through an Abbreviated New Drug Application (ANDA) in the United States, there is no clear statutory regulation to allow a similar expedited approval for biopharmaceuticals. In fact, legislation governing biologics is currently being debated throughout the world considering the large market for follow-on biologics. According to innovator companies, biopharmaceuticals differ from small molecules on the grounds of structural heterogeneity, immunogenicity, and manufacturing processes, and thus cannot be approved by an abbreviated review.

Various factors are affecting the acceptance or clarification of a regulatory framework to approve biogenerics. The largest factor affecting the development of these regulations is the establishment of bioequivalence of the biogeneric to the innovator drug. While it is easier to determine the period in which small molecules are absorbed into the body and metabolized, biopharmaceuticals are very difficult to characterize. Conformational changes and post-translational modifications such as glycosylation are believed to affect the function of the biologic. It is unlikely to have a framework for approving biogenerics without resolving the issues of 'sameness', bioequivalence, and safety and efficacy.

REGULATORY FILING STRATEGIES FOR APPROVAL OF BIOGENERICS:

A biologic is a prophylactic or a therapeutic substance that can be made only by a living substance and has a large, complex, heterogeneous molecular structure. The U.S. FDA approves new drugs under mechanism found in section 505 of the Federal Food, Drug and Cosmetic (FD&C) Act and approves most biological products under section 351 of the Public Health Service (PHS) Act. The Hatch-Waxman Act, which provides the ANDA approval, is only available to drugs approved under the FD&C Act and not to those products under the PHS Act. As of today, there are a few potential regulatory filing strategies for biogenerics or follow-on biologics: a 505(b)(2) application, a Biologics License Application (BLA), a Canadian New Drug Submission (NDS) or a European Marketing Authorization Application (MAA).

Section 505(b)(2) appears to be another type of NDA, that theoretically allows for expedited review of a follow-on therapeutic. Section 505(b)(2) applies only to those drugs that cannot be brought under an ANDA. A 505(b)(2) application also requires the submission of 'full reports of investigations, which have been made to show whether or not such drug is safe for use and whether such drug is effective in use pursuant to section 505(b). The 505(b)(2) applicant thus relies on the investigations conducted by someone else, including the original holder of the NDA-approved drug, and may be required to supply clinical data describing any deviations in safety and efficacy of the

new drug from the listed drug. This is not required in an ANDA.

RECENTLY APPROVED BIOGENERICS

The case of Berlex Laboratories Inc. v. Food and Drug Administration has played an instrumental role in developing a regime for the approval of generic biologics.

Betaseron, a Berlex interferon beta-1b product was approved for multiple sclerosis on July 23, 1993, and was awarded seven years of market exclusivity under the Orphan Drug Act (ODA). Biogen, who was developing several interferon beta-1a products during the 1990s, had developed BG9015, which had successfully completed clinical trials but had not been marketed, because Bioferon, a Biogen joint venture, had gone bankrupt. Biogen sought approval of Avonex, without conducting any clinical trials of Avonex, on the basis of comparability to BG9015. Initially, the FDA rejected Biogen's initial attempt to prove the equivalence of Avonex to BG9015, as the specific activity of Avonex was greater. Biogen then reformulated Avonex, proved physicochemical comparability, similar glycosylation, identical peptide mapping, and equivalent pharmacokinetics in humans compared to BG9015. The FDA used this evidence as being supportive, claiming that the clinical data generated by BG9015 would support the license for Avonex.

Avonex could not be sold without violating the ODA marketing exclusivity of Betaseron, unless Avonex was found to be not the "same" as Betaseron. Avonex contains 166 amino acids and is glycosylated, while Betaseron is missing the N-terminal methionine and contains 165 amino acids and is non-glycosylated. In April 1996, three weeks before approving Avonex, the FDA provided an important guidance document, claiming more flexible approval of biologics by allowing "manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy." Though the FDA was concerned that manufacturing changes could translate into significant changes in safety or efficacy, it stated that comparability would serve as an adequate assurance. Comparability protocols could include analytical chemistry, bioassays, pharmacokinetics, animal toxicity, all the way up to clinical trials, though no standard of review was stated. Thus, the FDA did allow the approval of Avonex, based on comparability to Betaseron, without additional clinical trials. Berlex challenged FDA on several grounds, but was unsuccessful in having Avonex's approval declared unlawful. Berlex means that pharmacologically and therapeutically equivalent biologics are a reality.

ESTABLISHING BIOEQUIVALENCE, SAFETY AND EFFICACY

Specifications submitted for approval of biologics are linked to analytical procedures, preclinical and clinical studies, and manufacturing processes, and must account for the stability of the biologic.

The Berlex case proves that clinical trials are not always needed to detect differences that might impact safety and efficacy. There is debate over whether a pharmacokinetic study is always needed, since present analytical methods are insufficient to support applications for generic biologics. Pharmacokinetic / Pharmacodynamic studies must be carefully designed, based on the product, known interactions, toxicities, as inherent flaws in the studies may result in an invalid study design, including wasted money and time.

Another criteria that presents challenges is purity, including absolute and relative purity of the biologic, as determining purity is largely method-dependent. Due to unique biosynthetic production processes and molecular characteristics of biologics, the drug substance can include several molecular entities or variants. When these molecular entities are derived from anticipated post-translational modification, they are part of the desired product. When variants of the desired product are formed during the manufacturing process and/or storage, and have properties comparable to the desired product, they are considered product-related substances and not impurities. Thus, if a standard including all properties to be compared can be established, determination of purity of a biologic can be further simplified for approval purposes.

Innovator companies contend that without identical processes and analytical methods used by the innovator companies, generic companies cannot provide therapeutically equivalent biopharmaceuticals. Innovator companies feel that comparability protocols are not sufficient, since analytical techniques used today are not able to measure or ascertain small changes in a process, which may affect the efficacy or clinical safety of the biologic. However, this argument seems to apply only to generic manufacturers, and not to the innovator companies, who later improve their processes over time using comparability protocols.

PATENT EXCLUSIVITY AND PATENT INFRINGEMENT:

A large challenge for biogeneric manufacturers is to be sure they are not infringing the innovator's patents. Generic companies find it difficult to establish the priority date for a particular biopharmaceutical drug, since the drug could be protected by about 30 to 90 patents in some cases. Screening and designing around patents for formulations, method of use, and processes, makes it harder to develop a non-infringing biogeneric, unless the requirement for identical processes of manufacture can be clearly ruled out. Another reason for concern is that Section 505(b)(2) does not allow for a patent challenge, as does an ANDA.

NEARING THE HORIZON - APPROVAL FOR BIOGENERICS

The Berlex case has played a pivotal role for the approval of biogenerics; the

case counters the historical claim that the production and regulation of biologics is completely dependent on manufacturing controls.

The approval pathway for biogenerics is certainly on the horizon. While the FDA has the scientific prowess and ability to approve a drug on the grounds of comparability, a deeper understanding of the criteria needed to establish bioequivalence, and the association of these criteria with clinical safety and efficacy, would certainly provide a regulated pathway for approving biogenerics. New developments in analytical techniques will certainly make this process easier. With the approval of biogenerics, the biopharmaceutical and biotechnology companies would not only have to prepare for the launch of biogenerics and expect price erosion, but will also have to take greater care to protect their intellectual property while formulating out-licensing and co-development efforts with their partners. For generic manufacturers, well, the horizon is not far away.

ABOUT NISHITH DESAI ASSOCIATES

Nishith Desai Associates, an international legal, tax and business counseling firm focuses on selected practice areas including the pharmaceutical and biotechnology industry. The firm's primary practice areas are international finance and tax, corporate and securities law and intellectual property law.

Bio Sketch

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