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Follow-on Biological Products— Legal Issues

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The scientific, regulatory, and legal framework for the approval of small-molecule generic drugs is well developed. Generic drugs are defined as products containing the same active ingredient as the branded drug, but likely having different inactive ingredients. In order to be marketed, the generic drug must have the same quality, efficacy, and safety as the branded drug. In contrast, marketing requirements for generic biologics, or follow-on biological products is unknown.

Many biologics, including blockbusters like Epogen/Procrit, are nearing patent expiration, and generics manufacturers, including Sicor (acquired by Teva), Barr Laboratories, and Ivax Corporation, are hoping to market generic biologics. Follow-on biologics, such as insulin, human growth hormone, and granulocyte-colony stimulating factor already have been marketed in third world nations. In the U.S., more than ten companies are attempting to develop generic versions of erythropoietin; Sandoz has applied for marketing of generic version of recombinant human growth hormone; and generic versions of insulin, human growth hormone, interferon -2b, and G-CSF are in development. The legal framework under which follow-on biologics could be marketed is addressed herein.

DEFINITION OF BIOLOGICAL PRODUCTS

The definition of a biologic has changed over time. In the U.S., a biological product is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenanaine, or derivative of arsphenamine) or any other trivalent organic arsenic compound), applicable to the prevention, treatment or cure of a disease or condition of human beings” (Public Health Services Act 42 U.S.C. § 262(i)). By statute, biological products include viruses, therapeutic sera, toxins and antitoxins, vaccines, blood, blood components or derivatives, allergenic products, any analogous products, and arsphenamines used for treating

disease. The statute does not offer a definition of “biologic,” but is fairly broad. The inclusion of the term “analogous products” makes the definition particularly broad since the basis for determining analogous products is not provided by the statute.

EXISTING LEGAL BASIS FOR APPROVAL OF BIOLOGICS

Two U.S. statutes apply to the regulation of biological products, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 *et seq*) (FFDCA), and the Public Health Services Act (42 U.S.C. § 262) (PHSA). The U.S. regulations charge the FDA with the protection of public health in part by ensuring that human drugs and biological products are safe and effective. The FDA administers the FFDCA and PHSA (among other statutes). FFDCA applies to all drugs and medical devices, and PHSA applies to “biological products.” Marketing approval under the FFDCA is by means of a New Drug Application (NDA) while approval under the PHSA is by means of a Biologics License Application (BLA).

Both drugs and biologics are subject to Investigational New Drug Application (IND) regulations. Pre-clinical research on new compounds is carried out in a laboratory, using a wide variety of techniques. Promising candidates are then studied in animals, and, subsequently, various clinical studies in humans are carried out following strict guidelines:

Phase I: A small number of healthy volunteers is given the compound to determine mainly that the drug is safe for human use.

Phase II: A small number of patients is given the medicine to assess its efficacy and safety and to ensure that there are no unacceptable side-effects.

Phase III: A large number of patients, usually thousands, take the medicine under supervision over a defined period of time, with the results used to establish efficacy.

If the results show the drug to be efficacious and safe, the data are presented to the FDA. The FDA reviews the data,

and if the data is acceptable, a marketing authorization is issued. Alternatively, the FDA may request additional studies or reject the application.

Following the grant of marketing authorization, the drug product is studied in large numbers of patients in hospitals and clinics to further assess its clinical effectiveness. This stage is called Phase IV or post-marketing study. Safety Assessment of Marketed Medicines (SAMM) studies help identify any unforeseen side effects.

In order to be marketed, a biologic requires only proper labeling and an approved BLA that indicates the product has been determined safe, pure, and potent, and that the manufacturing facilities meet the requirements to ensure safety, purity, and potency. Though biologics have traditionally been subject to much more scrutiny in manufacturing than drugs, those differences are being eroded.

Biologics have been approved under FDCA and PHSA, thus, both NDA and BLA applications have been submitted for biologics. The exceptions are glucagon and follistim that were approved under § 505(b)(2), and insulin, which was approved under its own statute for a time. The default approval pathway for biologics now is a BLA, unless the product is a hormone, in which case §505(b) is used.

MECHANISMS FOR FDA APPROVAL OF FOLLOW-ON-BIOLOGICS

Three major pathways exist by which a generic version of a previously approved drug (“branded product”) can secure FDA marketing approval, namely:

- A. New Drug Application (NDA) or Biologics Licensing Application (BLA)
- B. Abbreviated New Drug Application (ANDA)
- C. FDCA § 505(b)(2) Application

A. NDA or BLA

The new drug application route (FDCA § 505(b)(1)) is available for FDA approval of all molecular entities, regardless of whether the FDA has previously considered the safety and efficacy of that molecule. However, filing an NDA or BLA undercuts the purposes of a generic drug. These new applications require detailed investigations of safety and efficacy, including clinical studies outlined above. Thus, large monetary investments would be required that have to be recouped. The resulting product would not result in lower priced drugs, and the time required to complete the

trials would delay the introduction of generics as soon as the patent expires. Therefore, NDAs have rarely been used for approval of generic drugs. Consequently, it is extremely unlikely that a full NDA or BLA would be filed for a follow-on generic, though these remain as options, especially if other routes are not available.

B. ANDA Application

The Hatch-Waxman act has provided the ANDA approach for the marketing of a generic drug. In order to utilize the ANDA process, the generic manufacturer must demonstrate that its product is pharmaceutically equivalent to the branded product, i.e., it has the same amount of the same active compound(s) administered in the same dosage form. Thus, the generic product has to be equivalent to the branded product in *in vitro* and *in vivo* tests. The *in vitro* tests measure the rate of release of the active compound(s) in solution, while the *in vivo* tests measure the bioavailability of the product, i.e., the rate and extent of absorption of the active compound(s) into the blood stream of the subjects in pharmacokinetic studies.

The generic product is approved if the differences between the branded product and the generic product are within acceptable limits with respect to the levels of impurities and release rates of the active compound(s). If the *in vitro* and *in vivo* data for the generic and the branded drug are similar, then the pre-clinical and clinical data of the branded product is extrapolated to assess the generic product. The two products will be treated as therapeutically equivalent and the generic product may be used interchangeably with the branded product.

The ANDA process could be utilized for biologics that were originally approved under FDCA. Biotechnology companies maintain that the ANDA process cannot be applied to biologics because “the process is the product.” They argue that biologic products are harder to define chemically, and their characteristics may be dependent on the way they were expressed, purified, and manufactured, therefore, even minor modifications, such as changes in culture media or growth conditions, will have a major impact on the end-product. However, recent experience suggests that the process is not the product and ANDA is an appropriate route for the marketing approval of a significant number of follow-on biologics for several reasons.

First, the FDA issued, and the biotechnology industry advocated, the 2003 Comparability Protocols Guidance. The Guidance allows manufacturers to make manufacturing changes without performing additional clinical studies

to demonstrate safety and efficacy. The Guidance provides details for submitted comparability protocols for biologic products to demonstrate safety and efficacy, to establish comparability between a product made before a manufacturing change and a product made after a manufacturing change. The same guidelines could be used by a generic company to show that their biological product is similar to the branded product.

Second, only a very small number of biologics cannot be characterized at present, and analytical chemistry is progressing rapidly. The definition of biologic drugs includes biological macromolecules, polysaccharides, polynucleotides (DNA, RNA), and polypeptides (proteins). Nucleic acids and proteins, like small molecules, can be extensively characterized because their exact nucleotide or amino acid sequence can be determined. Nucleic acid-based technologies include gene therapy, antisense oligonucleotides, DNAszymes, ribozymes, and siRNA (RNAi). Because the precise chemical structure of the active substances of nucleic acid-based technologies can be characterized, process is not the product for them.

A number of therapeutic peptides contain eight to ten amino acids and are analogs of endogenous hormones including oxytocin, arginine vasopressin (ADH) somatostatin, gonadotropin releasing hormone, and luteinizing releasing hormone. Because of their small size, these peptides can be synthesized chemically, and virtually all of them are approved via NDAs. Therefore, process is not the product for small peptides, and they could be approved under an ANDA.

The peptides of intermediate complexity contain 20-50 amino acids, and include insulin, glucagon, teriparatide, nesiritide, enfuvirtide, refludan, and sermorelin. These peptides contain between 20 and 70 amino acids. They are mimics of endogenous proteins, and also generally are not glycosylated, therefore, immunogenicity concerns are lower. Thus, process is not the product for small peptides, and they could be approved under an ANDA.

Recombinant protein-based therapeutics include interleukins, deoxyribonuclease, replacement enzymes for metabolic disease, growth factors like granulocyte-colony stimulating factor, platelet derived growth factor, and the like. Some of these undergo post-translation modifications that could be difficult to characterize and replicate. Further, there are immunogenicity concerns since they are novel

proteins. However, these are a small part of “biologics” and thus, the exceptions should not make the rule.

Therefore, in some cases, ANDA is functionally not applicable to biologics. Further, ANDA is legally not applicable to biologics approved under the BLA. Thus, ANDA has limited utility for the approval of follow-on biologics. However, since the process is not the product for the majority of biologics, appropriate legislation should be passed to implement ANDA for biologics.

C. Section 505(b)(2) Application

The Hatch-Waxman Act implemented ANDA and § 505(b)(2) are complementary routes to approval of a generic drug. ANDA is functionally and legally not applicable to nearly all biologics and proteins, thus, § 505(b)(2) might be the only pathway by which the FDA could conceivably review applications for follow-on biologics.

Section 505(b)(2) is essentially a hybrid of NDA and ANDA that theoretically allows for expedited review of a follow-on biologic, and applies to drugs that can not be brought under ANDA. A § 505(b)(2) application 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 § 505(b). The major difference between NDA and § 505(b)(2) is that NDA applicant has conducted the appropriate studies and trials, while a § 505(b)(2) applicant relies on investigations conducted by someone else-including the original sponsor of an NDA-approved drug. However the § 505(b)(2) applicant must substantiate the “relevance and applicability” of previous findings to the current application and could be required to supply clinical data describing any deviations in safety and efficacy of the new drug from the listed drug. Finally, §505(b)(2) is arguably available to all small molecules, protein-based therapeutics, and biologics given both its broad references to drugs and deletion of the ANDA’s concept of “sameness.”

An issue with using § 505(b)(2) is that FDA would have to compare the clinical, CMC, and commercial data and information provided in the NDA or the BLA with the data provided by the generic company to approve the follow-on biologic. Traditionally, FDA has considered this information to be trade secrets. Secondly, U.S. law provides 5 years of data exclusivity (10 years in the EU) from the day of registration of the drug. It is not clear whether the innovator’s data could be legally used to approve generic products. In fact, treating the submitted data as trade

secret, and the use of data-exclusivity are becoming the dominant IP protection for branded biologic products.

The data included in the registration file of a pharmaceutical product, and disclosed to the FDA is used to approve the drug for market use. The U.S. regulations providing for 5 years of data exclusivity does not provide any exceptions, such as the use of the data to approve a generic. Therefore, the data provided in the NDA or the BLA cannot be used to approve follow-on biologics during the 5 years.

The FDA has traditionally considered the data provided in the NDA or the BLA to be trade secrets, and safeguards the information through non-disclosure. One aim of non-disclosure is to ensure that rival companies, including generic companies, do not gain access to the registration file of the original product. The biotechnology companies have advanced a second aim of non-disclosure, namely to prevent the FDA from relying on the registration file of an original in order to compare it to the chemical and toxic levels of a potential generic substitute. They argue that practically there is no difference between the use of the data to approve a generic and the disclosure of the data.

The position of the biotechnology companies may not be correct. First, several statutory provisions evidence the Agency's authority to rely on information in addition to the data submitted in the generic application when determining safety and efficacy. Congress granted FDA the authority to carry out the Agency's mission, including the authority to promulgate regulations governing the approval of drug and biologic products. Second, no statute appears to explicitly state that the information is protected as trade secret and cannot be internally used by the FDA. Third, applying trade secrets law would extend the protection provided by the data exclusivity regulations, thereby raising anti-trust issues.

Even if the submitted information was a trade secret, the Supreme Court has expressly held that the Trade Secrets Act "cannot be construed as any sort of assurance against internal agency use of submitted data during consideration of the application of a subsequent applicant for registration." *Ruckelshuus v. Monsanto Co.*, 467 U.S. 986, 1009 (1984). In that case, the Court held that the EPA did not violate the Trade Secrets Act when it considered the data of one applicant in connection with the application of another. Applying the Court's ruling, the FDA can internally rely on previously submitted safety and efficacy data in the consideration of generic biologics. Thus, § 505(b)(2) appears to be the only pathway by which the FDA could conceivably review applications for follow-on biologics.

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