

Towards Understanding the “Generic” Debate about Biologics

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ABSTRACT

Much has been written debating different aspects of the same controversial topic variably known as “generic biologics,” “follow-on biologics,” “follow-on biotechnology products,” “follow-on therapeutic proteins” and “generic biopharmaceuticals.” Many considerations pertaining to various legal, scientific, economic, policy and social issues involving the legislative, executive, and judicial branches of the government are relevant though the debate is especially complicated because of definitional and interpretative problems. Further, the controversies themselves are often confused and confusing due to the use of different terminology. While this article cannot clarify or simplify in the limited space available all of the complexities, it is designed to further understanding of the multiple issues related to the “generic” debate about biologics.

INTRODUCTION

The current issues surrounding the “generics” debate exist because many biologics, often made by modern biotechnology methods such as recombinant DNA, are nearing the end of their original patent protections. The possibility thus arises of generic competition, as is provided in the context of the traditional scheme embodied in Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 amendments (Waxman-Hatch Amendments)¹ to the Federal Food, Drug, and Cosmetic Act (FD&C Act)² for products regulated under the FD&C Act. The debate has become more intense because the Food and Drug Administration (FDA) has made several announcements that it is planning to issue a guidance document on follow-on biologics but has yet to do so.

This article is not intended to nor to present all aspects of the debate; rather, it provides some of the key legal and scientific underpinnings of the controversies, with a few brief concluding observations and commentary.

BIOLOGICAL AND NON-BIOLOGICAL DRUGS: REGULATORY OVERSIGHT

The confusing nature of the current debate is related to the interplay between different statutory schemes for biologic and non-biologic drug regulation,³ and to the ill-defined nature of biologics from both a legal and scientific standpoint. Biologics are a special class of drugs, if they are used for therapeutic/prophylactic purposes, and they are

medical devices, if they are used for diagnostic purposes. Even though historically biological drugs have been regulated very differently from other drugs, more recently, particularly with the recent transfer of responsibility for the review of many therapeutic biologics from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research, certain aspects of biological drug regulation have become the same as or similar to other drug regulation. Of importance here, however, are the differences. The most important difference is that biologics licensed under section 262 of the Public Health Service Act (PHS Act)⁴ are not subject to Title I. Section 262, which contains no parallel provisions to those in Title I, provides for the marketing of biologics by obtaining FDA approval of a biologics license application (BLA). It therefore becomes important to understand what products are and are not biologics.

Biologics include vaccines and blood products (including blood). The use of modern biotechnology has expanded the types of biological drugs to include cytokines, such as interferons, and monoclonal antibodies. Although often it has been stated that biologics are the products obtained or sourced from living organisms, this is technically not correct according to FDA's definition of a biologic. Antibiotics and hormones such as insulin and human growth hormone (hGH) are not biologics, even though traditionally they have been obtained from organisms such as microbes and animals, including human beings. This emphasis on source, however, is not entirely misplaced since FDA's regulations defining biologics allude to source, as well as to other differing criteria, such as whether a product acts through a specific

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immune process.⁵

Another characteristic of biologics, especially traditional biologics such as vaccines, is that they are products that are difficult to characterize or define. They are complex mixtures including large molecules called macromolecules composed of proteins containing components or building blocks of amino acids. Sometimes the amino acids have attached to them carbohydrates or sugars, resulting in products called glycoproteins or glycosylated proteins. Slight natural variations in the carbohydrate parts of such proteins can produce different proteins called isoforms. Thus, biologics typically have been defined in terms of their method of manufacture, including their source materials. FDA has over the past several years developed guidance documents, called comparability guidances,⁶ to help biologics manufacturers establish product comparability based on analytical or other laboratory studies or based on limited clinical evaluations to avoid conducting full clinical studies after changes are made in the manufacture of a licensed biologic.

The basic FD&C Act approval mechanisms to commercialize non-biological drugs, such as insulin and hGH, involve three different types of new drug applications (NDAs). First, “full NDAs,” described in section 355(b)(1), which contain full reports of investigations related to pre-clinical, clinical and other requirements for approval, are often submitted by R&D-based companies for drugs not marketed before, typically called pioneer, brand name, or innovator drugs; and, second and third, 355(b)(2) and 355(j) applications, based on sections of the FD&C Act that describe them.

The 355(j) provision, which governs abbreviated new drug applications (ANDAs), and the section 355(b)(2) provision, both generally provide the conditions for approval of duplicate or related versions of approved innovator drugs whose patents have expired, will not be infringed, or are challenged as invalid. Such approvals may be obtained without the submission of all of the safety and effectiveness information required of the innovator submitting a section 355(b)(1) application. These Title I provisions are supposed to stimulate competition by decreasing the time and costs associated with bringing competitive drugs to market and thereby provide the public with lower priced drugs.

ANDAs are permitted for a drug product that is the “same” as a drug product listed in FDA’s Approved Drug Product List with respect to active ingredient(s), route of administration, dosage form, strength, and conditions of use recommended in labeling.⁷ ANDAs can also be submitted for a drug product with certain changes from a listed drug if FDA has approved a petition permitting the submission of an ANDA for the changed drug product.⁸

Bioavailability information comparing the rate and extent of absorption of the test drug and listed drug is generally all of the clinical information that is required for approval of an ANDA.⁹

The conditions under which a section 355(b)(2) application can be submitted are more complex and have been a major source of the “generic” controversy. Innovator companies view it as an inappropriate way that FDA has developed through new interpretations to approve competitive protein products, such as insulin and hGH, that are “similar” to the macromolecular protein structures of many biologics. Thus, 355(b)(2) is seen as portending a path for approval of competitive drugs that are “biologic-like,” allowing copies of such drugs to be marketed without repeating all of the safety and efficacy studies required of the innovator drugs.

Generally, 355(b)(2) applications are appropriate for changes in approved drugs that cannot be approved through the submission of an ANDA, because investigations (other than bioavailability studies) are necessary to evaluate the safety and efficacy of the changed product.¹⁰ The additional investigations that can be relied upon in a 355(b)(2) application typically have been considered to be published literature or a combination of published literature reports and new clinical investigations.

The use of published literature as the basis for approval of a section 355(b)(2) application has been titled a “paper NDA,” which actually predates the enactment of the Waxman-Hatch Amendments.¹¹ In a draft guidance document FDA has said that

“Much has been written debating different aspects of the same controversial topic variably known as ‘generic biologics,’ ‘follow-on biologics,’ ‘follow-on biotechnology products,’ ‘follow-on therapeutic proteins’ and ‘generic biopharmaceuticals.’”

355(b)(2) applications also can be based on FDA’s finding of safety and effectiveness for approved innovator products.¹²

Another important aspect of FDA’s implementation of Title I is the agency’s therapeutic equivalence (TE) ratings.¹³ TE ratings are important because many states use such ratings for determining whether one drug may be substituted for another or whether a competitive product is the generic equivalent of a brand name product. Products determined by FDA to be therapeutic equivalents are assigned an “A” rating, whereas products shown not to be equivalent to a referenced drug are assigned a “B” rating. One drug is therapeutically equivalent to another if, in most relevant part, they are pharmaceutical equivalents in that they contain identical amounts of the same active ingredient in the same dosage form and route of administration and are bioequivalent, meaning that the rate and extent of absorption of the test drug does not show a significant difference from that of the listed drug.¹⁴

THE CONTROVERSIES

The legal and scientific challenges have largely been, respectively, in the form of innovator rights to safety and

effectiveness data and FDA's ability to approve under section 355 competitive versions of approved "biologic-like" macromolecular protein products, in particular hGH. Embedded in these considerations, on the legal side, is the protection of proprietary information and, on the scientific side, what is "sameness."

The Biotechnology Industry Association (BIO) argues that, on scientific grounds, FDA cannot approve ANDAs for competitive versions of therapeutic innovator proteins.¹⁵ They are complex products comprised of many active components, both known and unknown, making it difficult to definitively characterize the final product; therefore, since ANDAs rely on active ingredient comparisons of "sameness," such applications are not possible. It cites the non-biological drug example of Premarin®, a conjugated estrogen product obtained from the urine of mares for which FDA would not allow ANDAs for synthetic versions because of inadequate characterization of the active ingredients.

BIO also states that the science is not available to adequately characterize biologics in terms of product variants, thus raising a variety of safety and effectiveness issues, including increased immunogenicity and reduced clinical effectiveness. It therefore further argues that FDA has appropriately long interpreted the PHS Act as requiring full, original data for the licensure of each biologic, and that such a practice raises to the level of administrative common law, which cannot be changed without providing notice and opportunity for comment. BIO also argues that FDA's comparability guidances should not be utilized to compare the manufacture of an innovator's product to the manufacture of a competitive version because neither manufacturer has access to each other's manufacturing information.

BIO and others¹⁶ further disagree with the broad applicability of section 355(b)(2) applications, largely on legal grounds, stating that section 355(b)(2) is intended to allow approval based on published literature, not on FDA's finding of safety and effectiveness of an innovator product. Such reliance on innovator information essentially involves misappropriation of the innovator's trade secret and confidential business information, which is not permitted under the Takings Clause of the Fifth Amendment to the Constitution, among other arguments.

Most recently, this view of the limited coverage of section 355(b)(2) applications has been additionally challenged in the context of a particular product. The challenge involves hGH, and not a generic drug company, but an innovator drug company, Novartis AG through Sandoz, Inc., its generic affiliate. The debate concerns Pfizer's approved Genotropin® and Sandoz' pending application for Omnitrope™. Sandoz filed a section 355(b)(2) application for Omnitrope™, rather than a full NDA. Pfizer has therefore petitioned FDA arguing that it is legally improper for FDA to rely on, reference, or otherwise use information establishing the safety and efficacy of Genotropin® to approve Omnitrope™; further, it is asserted that there are significant compositional and manufacturing differences that preclude the scientific reliance on Genotropin® data to support

approval of Omnitrope™.¹⁷ Pfizer also states that, for legal and scientific reasons, Omnitrope™ does not meet FDA requirements to receive an "A" rating. "A" ratings can only be assigned to drugs approved under section 355(j), not 355(b)(2), Pfizer argues. Moreover, it alleges that Omnitrope™ has a different weight, is produced differently, and cannot be determined to be pharmaceutically equivalent to Genotropin® because of the inadequacy of analytical tests to determine "sameness."

Not surprisingly, the Generic Pharmaceutical Association (GPhA) and its member companies, such as Barr Pharmaceuticals, present opposite views. GPhA argues that since many biologics are drugs subject to regulation under the FD&C Act, FDA has the authority to approve section 355(b)(2) applications for a generic biological drugs.¹⁸ GPhA further urges FDA to adopt procedures mirroring the paper NDA procedures applied to drugs prior to 1984, stating that FDA should amend its regulations to include a paper BLA approach. FDA can also assign "A" ratings to generic biologics approved under section 355(b)(2) or approved through the paper BLA process, contending that there is nothing legally to prevent FDA from giving biogenerics such ratings, which would make them substitutable by pharmacies. GPhA also points out that FDA has previously approved some biologics under the PHS Act without the submission of a full data package.¹⁹ Barr additionally believes that some products approved through the BLA process may have been misclassified as biologics.²⁰ The technical and scientific challenges of characterizing macromolecules are argued not to be that formidable, since biotech companies make changes in their formulations and submit comparability data that result in FDA approval. Thus, the notion that biologics cannot be adequately characterized is a myth.

Thus far, FDA has formally commented on primarily one aspect of the debate. In a consolidated response²¹ to various citizens petitions and comments regarding FDA's construction of section 355(b)(2), the agency declines to alter its interpretation. It states that its long-standing view has been that section 355(b)(2) does not require the conduct of new studies to demonstrate what has already been demonstrated. The structure of the Waxman-Hatch Amendments, the language of section 355(b)(2), the purposes of Title I, and policy considerations support the agency's position, FDA argues. The agency further notes that such applications have been used to approve more than 80 products, that over 30 additional such applications are currently pending, and that most of the applications have not been solely literature-based.

FDA also denies that its interpretation of section 355(b)(2) amounts to an unconstitutional taking of property without adequate compensation. Given its long-advocated pronouncements of the broad scope of section 355(b)(2), especially as outlined in its proposed and final regulations implementing Title I, FDA states that BIO and others do not have a requisite expectation to make a valid takings argument.

The agency does agree, however, that it may not assign an “A” rating to a drug product unless, in relevant part, it is pharmaceutically equivalent and bioequivalent to a listed drug. Such would not be the case, it says, if the drug were a different salt form of an approved listed drug.²² Press reports indicate, too, that FDA agrees it may not rely on innovator data contained in a BLA to approve a competitive product.²³

OBSERVATIONS AND COMMENTARY

Notwithstanding the complexity of the debate and the diversity of viewpoints, FDA appears clearly headed towards the development of a more formal scientific paradigm for evaluating product similarities or sameness of complex macromolecules. Also, Congress seems likely to jump into the debate, having already conducted a few limited hearings on the subject.²⁴ The question therefore seems not whether, but when and how, will FDA and Congress implement a comparative regime for proteins and other macromolecules? Although FDA initially planned to issue its follow-on biologics guidance by early summer, the agency has now stated that the guidance will not be published until after a public scientific workshop is held sometime this year. The guidance will apparently contain a description of various “follow-on proteins” and their routes of approval, in order to help the agency establish a consistent scientific approach.

The importance of FDA’s developing this aspect of its initiative can be best illustrated in terms of examples of different types of biologic-type molecules that have been approved under the FD&C Act using different regulatory mechanisms. These include calcitonin (salmon) (composed of 32 amino acids) and desmopressin (9 amino acids), both relatively small protein drugs; insulin (51 amino acids); and hGH (191 amino acids). In the case of calcitonin, section 355(b)(2) or ANDA applications have been submitted and in the case of hGH, a 355(b)(2) application has been submitted, as discussed previously. ANDAs have been approved for desmopressin, which is chemically synthesized. Other different examples of approved non-biological drugs include Premarin®, a non-protein hormone product, for which FDA would not permit an ANDA, as discussed previously, but ultimately did approve a 355(b)(2) application, and Perganol®, another hormonal product also obtained from urine (of post-menopausal women) composed of two protein hormones making up less than 5% of the product, with the remainder composed of mostly uncharacterized urinary proteins. In the latter case, FDA approved an ANDA for a competitive product and assigned an “A” rating to it, a decision that was challenged in court. Even though the two products had different glycoprotein isoforms, the court upheld FDA’s position.²⁵ It agreed with

FDA’s view that since any potential differences in isoforms were not clinically significant, clinical identity rendered the products the “same” for purposes of section 355(j).

These examples illustrate that FDA’s scientific and regulatory treatment of certain smaller proteins and more complex macromolecular products seemingly has been variable and inconsistent. Such regulation appears to have been molecule-dependent, which will likely continue to be the case with more complex “biologic-type” macromolecules. Nonetheless, it seems difficult to reconcile that, on the one hand, different salts of the same active ingredient cannot be “A” rated because they are not pharmaceutically equivalent, whereas, on the other hand, different isoforms of glycoproteins can be “A” rated because they are clinically equivalent.

This type of differential treatment of smaller molecule and macromolecular products transcends whether a drug is classified legally as a biologic. The treatment relates to the fundamental **legal** meaning of “sameness.” It also seems reminiscent of the way FDA eventually handled the market exclusivity provisions of the Orphan Drug Act pertaining to “sameness.” After much initial confusion about what scientific criteria to apply,²⁶ the agency eventually adopted a combination of chemical and clinical tests for “sameness.”²⁷ In any event, consistent, transparent scientific

approaches are key to any regulatory scheme of drug regulation.

Another important aspect of these discussions is that, even with the advent of a regulatory path for the approval of generic biologics, the market paradigm for such drugs may not neces-

sarily be the same as that for traditional generics. The barriers to market entry could be much higher, in part because approvals could be more molecule-dependent and thus more variable, and because clinical testing beyond bioavailability studies may often be necessary. Both of these testing considerations would drive up testing costs. Also, the establishment of production facilities for complex macromolecules may be more capital-intensive. These types of barriers might not only enable branded drug manufacturers preferentially to enter the biogenerics marketplace, but also enable them to become major constituencies of the generic industry.

Finally, substitution or interchangeability also is an important aspect of the traditional generics market paradigm. Typical generic companies often do not need sales and marketing departments since their products can be substituted for innovator drugs. If follow-on proteins or other similar products are not assigned “A” ratings or other measures of substitutability, the types of competitive drugs that are developed could be significantly altered, a development that could again favor the entrance of branded manufacturers into the generic marketplace.

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ENDNOTES

1. Pub. L. No. 98-417, 98 Stat. 1585 (1984).
2. Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301-397 (2000). All textual references to sections of the FD&C Act and to other statutes are to the laws as codified.
3. For an extensive discussion of biologics regulation, see Edward L. Korwek, Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000, Special Issue Celebrating the Journal's 50th Anniversary, Food and Drug L. J. 123 (1995).
4. Ch. 288, 37 Stat. 309 (1912), as amended at 42 U.S.C. § 262 (2000).
5. See 21 C.F.R. § 600.3(h) (2004).
6. See Food and Drug Administration, Center for Biologics Evaluation and Research, Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (April 1996), 61 Fed. Reg. 18612 (1996) (announcing availability of the guidance); Food and Drug Administration, Center for Biologics Evaluation and Research, Draft Guidance on Comparability Program Protocols: Chemistry, Manufacturing and Controls Information (Feb. 2003), 68 Fed. Reg. 8772 (2003) (announcing availability of the guidance).
7. 21 C.F.R. § 314.92.
8. *Id.* § 314.93.
9. *Id.* § 314.94(a)(7).
10. See *id.* § 314.54(a).
11. See FDA, Publication of “Paper NDA Memorandum,” 46 Fed. Reg. 27396 (1981).
12. Food and Drug Administration, Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (Oct. 1999), 64 Fed. Reg. 68697 (1999) (announcing availability of the guidance).
13. See generally Approved Drug Products With Therapeutic Equivalence Evaluations, US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research (24th Ed.).
14. *Id.* section 1.2.
15. Citizen Petition, Biotechnology Industry Organization, Follow-On Therapeutic Proteins, No. 01P-0323 (April 23, 2003).
16. See, e.g., Pharmaceutical Research and Manufacturers of America, Comments on Draft Guidance for Industry on Applications Covered by Section 505(b)(2) (April 3, 2000).
17. Pfizer, Inc., Citizen Petition Requesting FDA Rejection of Omnitrope® (May 13, 2004).
18. Letter from Bill Nixon, President, Generic Pharmaceutical Association, to Daniel Troy, FDA (Jan. 18, 2002).
19. United States Senate, Committee on the Judiciary, “The Law of Biologic Medicine,” Testimony of Mr. William Shultz on behalf of the Generic Pharmaceutical Association (June 23, 2004).
20. United States Senate, Committee on the Judiciary, “The Law of Biologic Medicine,” Testimony of Dr. Carole Ben-Maimon, President, Chief Operating Officer, Barr Laboratories (June 23, 2004).
21. Food and Drug Administration, Consolidated Response re Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1 and 2003P-0408/CP1 (Oct. 14, 2003).
22. *Id.* at p. 32 (referring to the fact that because paroxetine mesylate is a different salt, it will not be “A” rated with respect to paroxetine hydrochloride).
23. See ‘Follow-On’ Biologics Guidance Will Limit Use of Data to ‘Public Domain,’ F-D-C Rep. (“The Pink Sheet”), May 10, 2004, at 3.
24. See notes 19 & 20, *supra*.
25. Serono Laboratories, Inc. v. Shalala, 158 F.3d 1313 (DC Cir. 1998).
26. For a background discussion of the criteria FDA used before adoption of its orphan drug regulations, see Edward L. Korwek, Orphan Drug Trials and Tribulations: Profitability, Patient Ceiling, Market Exclusivity, AIDS, and Biotechnology, 3 Reg. Aff. 133 (1991).
27. 21 C.F.R. § 316.3(b)(13).

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