US rules on biosimilars - what has changed?

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On 30 May 2006, the United States Food and Drug Administration (FDA) approved the marketing of Sandoz' Omnitrope (somatotropin) for injection. The approval was based in part on data that had been submitted by Pfizer Inc. (Pfizer) to support the approval of its somatotropin product, Genotropin. Depending on one's perspective, the approval of Omnitrope was a significant first step toward approvals of biosimilars by the FDA or a fact-based approval that signals no important change in the FDA's attitude toward biosimilars. The former view is that of the generic industry (see for example the 31 May 2006 press release of the Generic Pharmaceutical Association at *www.gphaonline.org*). The latter is the analysis of the FDA, which sought to downplay the significance of the approval. While the innovator industry opposed the approval on many grounds by submitting citizen petitions to the FDA, it has not to date followed up on those petitions by suing FDA over the approval, perhaps suggesting a wait and see attitude concerning the implications of the FDA's actions.

It is undeniable that the Omnitrope approval represents an important development in the FDA's consideration of what it calls "follow-on protein products" and what are referred to in this chapter, using the European convention, as biosimilars. The Omnitrope approval was, however, a limited step, and its implications should not be overstated. In this chapter, we review:

- The reasons why biosimilars present more challenging issues for regulators than generic versions of non-biological drugs.
- The somewhat unusual statutory framework applicable to biological products in the US.
- The steps taken by both sides of the controversy concerning Omnitrope that preceded the approval.
- The limitations stated by the FDA in the documents it issued at the time of the approval.
- The important issue of approval versus substitutability.
- The implications of the Omnitrope approval for potential approvals of other biosimilar products under current law.
- The potential implications of this decision for legislative change in the US.

HOW DO BIOSIMILARS DIFFER FROM NON-BIOLOGICAL GENERICS?

A non-biological product generally contains as its active ingredient a chemical, usually a relatively small molecule, that is usually amenable to full physico-chemical characterisation. The active ingredient is formulated with appropriate inactive or inert ingredients into a dosage form to allow the active ingredient to be administered and absorbed into the patient's bloodstream. The rate and the extent of absorption into the bloodstream determine the therapeutic effect and clinical safety of the product.

The challenge for the manufacturer of a generic version of the innovator's reference product is to produce a product that will deliver essentially the same amount of that active ingredient to the bloodstream at roughly the same rate and extent as the innovator product. If it does so, and if there is nothing unsafe about the composition of the generic product, the generic manufacturer has succeeded in making a copy that can be confidently expected to duplicate the effects of the innovator.

It is therefore a general presumption that, provided there is no difference between the *in vitro* and *in vivo* performance of the generic copy as compared with the reference product, the copy product should be approved. Approval of a non-biological generic product is principally based on an assessment of the information on the manufacture and control of the active ingredient and the finished product and a determination of equivalence. The generic copy is said to be equivalent to the originator's product if the generic applicant satisfies two basic conditions:

- The generic product is pharmaceutically equivalent to the originator's product, that is, it contains the same amount of the active ingredient in the same dosage form that meets the same or comparable standards.
- The generic product and the originator's product should have a similar rate and extent of absorption into the systemic circulation against certain pharmacokinetic parameters, namely the area under the curve and the maximum plasma concentration.

The two products are conventionally considered to be bioequivalent if the measurements of these parameters meet certain tolerance limits set by the regulatory authorities.

In contrast, biological products tend to contain active ingredients that are structurally more complex than those of traditional non-biological drugs. In many cases it is difficult or nearly impossible to characterise the biological active ingredient by any means other than its biological effects. However, a single biological active ingredient can display multiple (pleiotropic) biological effects. Moreover, two components that produce the same effect on one parameter may produce different effects on another (causing them, for example, to be equally effective, but not equally safe). As a practical matter, the most reliable way to

assure that one batch of product will produce the same effect as another is for both batches to be manufactured in exactly the same way. Because the generic (biosimilar) manufacturer will not know the manufacturing process of the innovator, there is an obvious difficulty in producing a copy that can be counted on to produce the same effect. Further, impurities that result from a particular manufacturing process may have clinically harmful effects. As one important example, there is concern that differences between two products manufactured differently may result in the products producing different immunological responses in the body of patients. This is an important clinical safety issue that needs to be addressed during clinical development.

To a significant extent, it is recognised that the conventional approach to assessment of pharmaceutical equivalence and bioequivalence may not be adequate to determine the clinical safety and efficacy of biosimilars. Regulators, and the manufacturers themselves, recognise the difficulties discussed above and the risks that may be presented by unproven assumptions of equality between a biosimilar product and the innovator it copies. Because of this, regulators have demanded more evidence of actual clinical safety and effectiveness as a basis for approval for biosimilars than is traditionally required for non-biologic products.

US LAW APPLICABLE TO BIOSIMILAR APPROVAL

Analysis of the regulatory requirements for approval of biosimilar products in the US is complicated by a historical anomaly. The majority of protein products of biotechnology are approved under section 351 of the Public Health Service Act (PHSA) (*see box, Terminology in the US*). But the FDA approves some such products (for the most part, hormones or insulin) under the Federal Food, Drug, and Cosmetic Act (FFDCA) §505. There is no rational basis for the different treatment. It is based simply on what happened, well before the advent of biotechnology, when hormone and insulin products were first submitted to FDA for approval. (Other than the approval process, biologic products for therapeutic uses are regulated as drugs under the FFDCA.)

The statutory language of the approval provisions differs between the FFDCA and the PHSA. The FFDCA requires approval of a new drug application (NDA) based on evidence of safety and "substantial evidence" of effectiveness. The PHSA requires approval of a biologics licence application (BLA) based on proof that the product is "safe, pure, and potent". Nevertheless, approval of innovator products requires, under both, the submission of animal data and clinical trials proving safety and effectiveness.

The question of which statute applies is significant for biosimilar products. The FFDCA has a mechanism, termed an abbreviated new drug application (ANDA), for approval of generic drugs. In addition, the FDA has interpreted the FFDCA to allow it to rely, to an extent, on innovator data to support the approval of so-called "505(b)(2) applications" for products that are not true generics but instead are considered sufficiently similar to the innovator that the innovator data apply. In the case of both ANDAs and 505(b)(2) applications, the FFDCA includes significant protections for innovator companies, discussed below (*see The FFDCA*). For the PHSA, however, there has never been any generic approval process, nor are there offsetting protections for innovator manufacturers.

TERMINOLOGY IN THE US

A biological product is defined in the PHSA as:

- "A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine 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." (*section 351(i), PHSA, 42 U.S.C. §262(i) (emphasis added)*).

This definition has been interpreted by the FDA to include blood products, vaccines, and antitoxins, but also many proteins and other products of biotechnology.

The FFDCA

FDA has explicit statutory authority to approve a generic version of an innovator product (*FFDCA § 505(j)*). To qualify for approval, the generic must generally be shown to be the same as the innovator in the following ways:

- Active ingredients.
- Labelling.
- Strength.
- Dosage form.
- Bioavailability (that is, it must be shown to be bioequivalent).

In the FDA's response to the citizen petitions opposing approval of Omnitrope, it suggested that it has the authority to approve biosimilar products using the 505(j) route in appropriate circumstances. It did not, however, use this route with respect to Omnitrope.

A significant hurdle for biosimilar product approval under the 505(j) route would be the requirement that the products be shown to have the "same" active ingredient. The innovator industry's strongly held view is that the identity of the active ingredients of a biologic product is dependent upon and determined by the manufacturing process for that product. Therefore, innovators argue, it is not fair to say that two products manufactured by different manufacturers using different manufacturing processes have the same active ingredient.

With respect to Omnitrope, the FDA did not find that the ingredient of that product was the same as that of the innovator it copied (Pfizer's Genotropin). Instead, it concluded that it was highly similar. The FDA did argue that Omnitrope and Genotropin shared essentially the same molecular weight, rejecting a Pfizer assertion that the molecular weights differed.

The FDA also approves certain types of products pursuant to its "505(b)(2) policy". FFDCA §505(b)(2) places certain obligations on an applicant submitting an NDA that relies on investigations which are not owned by the applicant and to which it does not have a right of reference. Such an applicant must submit certifications addressing any patents on the drug for which those investigations were completed. Neither this provision nor any other part of the

statute states that the FDA can, in its review of any NDA, rely on data submitted by an innovator applicant or on the FDA's finding that the innovator applicant's product is safe and effective. Nevertheless, the FDA has taken the language of §505(b)(2) to mean it can approve a type of NDA that relies in part on data submitted by the applicant and in part on the finding that FDA has made that some other drug is safe and effective. The FDA's position is controversial. A challenge to that position by Pfizer with respect to another, non-biologic product is still pending in US District Court, though that litigation has been stayed now for some time because the FDA stayed the challenged approval.

The Omnitrope NDA was a 505(b)(2) application. The FDA, in approving that application, relied in part on the showing of safety and effectiveness of Genotropin, the Pfizer product. As is usual with a 505(b)(2) application, the FDA also relied on data, including clinical trials, submitted by Sandoz.

PHSA

There is no statutory procedure for approval of generic versions of products approved under the PHSA. Nevertheless, supporters of biosimilar approvals have argued that the FDA could, without statutory change, approve biosimilars that rely on prior approvals of innovators under the PHSA.

One theory is that, while the relevant PHSA language does not allow reliance on innovator data, it does not prohibit it. Therefore, it is suggested the FDA could, by administrative order, find the necessary evidence that a biosimilar is safe, pure, and potent by partial reliance on data submitted by the innovator or on the FDA's own finding with respect to the innovator product.

Another possibility mooted by some generic proponents is that for particular drugs the FDA might approve the biosimilars under the FFDCA, even though the copied innovator was approved under the PHSA. This might be accomplished by changing the BLA innovator approval to an NDA approval. That would then make the FFDCA routes to approval available for the biosimilar. Alternatively, the FDA might decide that the biosimilar product could itself be approved under the FFDCA, specifically as a 505(b)(2) application, even though the innovator remains approved under a BLA. Neither of these possibilities would find clear support in the statute.

The FDA, at the time that it approved Omnitrope, issued a question and answer document that stated its view that a pathway for approval of biosimilars would require new legislation (*see www.fda.gov/cder/drug/infopage/somatropin/qa.htm*). It is possible that the FDA could change its mind in the future, however it seems unlikely that it would do so without a change in the political party that controls the executive. That will not happen until, at the earliest, January 2009.

THE EFFORTS TO PERSUADE THE FDA TO APPROVE, OR NOT TO APPROVE, OMNITROPE

The FDA allows anyone seeking to persuade the FDA to take, or not to take, particular actions to file so-called citizen petitions. Those petitions, usually in letter form, are often similar to a legal brief in content. In many cases they are accompanied by documentary support and declarations of experts. The Biotechnology Industry Organization (BIO), Genentech, and Pfizer filed such petitions seeking, in whole or in part, to prevent the approval of Omnitrope.

The filing of a petition does not have any automatic effect in delaying or preventing the FDA action. However, the FDA commonly seeks to address the issues raised in citizen petitions before taking action. In this case, on the same day that it approved Omnitrope, the FDA issued a detailed response to the three petitions insofar as they related to Omnitrope. The petitions challenged the FDA's legal authority to approve the biosimilar application and challenged the scientific basis for the approval. The FDA had in 2003 issued a response in part to the BIO petition, insofar as it argued that there was no legal basis for FDA's 505(b)(2) application policy. The 2006 FDA response effectively incorporated the earlier response by reference.

The FDA response to the petitions illustrates one significant deficiency in the citizen petition mechanism for challenging a competitor's approval. Because NDAs are confidential until approved, the petitioner has no way to know exactly what is included in the application. Therefore, in some cases, the FDA was able to dismiss the petitioners' arguments by asserting that their factual assumptions about the Omnitrope approval were incorrect.

It seems that the FDA struggled with its decision to approve Omnitrope. Sandoz expressed significant frustration with the pace at which its application was being processed. That frustration ultimately led it to sue the FDA in the US District Court seeking an order requiring the FDA to decide. The courts are usually reluctant to interfere with the FDA's priorities in the review of marketing applications. Nevertheless, in this case, the court agreed with Sandoz and ordered the FDA to approve the application or to refuse approval and give Sandoz the administrative appeal rights provided by the statute for such a refusal. The FDA decision satisfied the court's order.

What the FDA did not decide

The FDA attempted to limit the significance of its decision to the single application before it in its response to the citizen petitions seeking to prevent the Omnitrope approval. The Omnitrope approval, it said, did not require it to address a number of the issues that the petitions posed. Specifically, the FDA said it did not need to address:

- **Arguments that a biosimilar product approval would require the use of trade secret data and information in the innovator application.** The FDA said that it was not required to review any such data in the Genotropin application, or in any other innovator application, to approve Omnitrope. Instead, the FDA said it relied on its own finding that Genotropin had been shown to be safe and effective.

- **Arguments relating to the legality of approval of a biosimilar product under the PHSA or under an ANDA.** At the same time that it issued the opinion, the FDA stated that such an approval under the PHSA would require legislative change. In the FDA denial of the related citizen petitions, it briefly addressed the potential for approval of an ANDA, noting that nothing in the statute would prohibit approval of an ANDA for a biosimilar product "as long as the current state of science allows the evaluation necessary to support approval" (*Petition Response at 45-46*).

- **Arguments relating to substitutability of Omnitrope for Genotropin.** The FDA said that Sandoz had not asked for a therapeutic equivalence rating for its product (*see below, Substitution of biosimilars*).

- **Scientific issues associated with protein products that have unknown or multiple active ingredients.** The FDA noted that Omnitrope has one active ingredient.

- **Scientific issues associated with proteins with an unknown mechanism of action.** The FDA stated that somatropin's mechanism of action is understood.

- **Scientific issues associated with proteins that are difficult to characterise.** The FDA said that the human growth hormone can be characterised using currently available technology.

- **Scientific issues associated with glycosylation.** Human growth hormone products are not glycosylated.

SUBSTITUTION OF BIOSIMILARS

In the US, the FDA identifies drugs that it finds to be therapeutically equivalent in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", but popularly known as the "Orange Book". (The Orange Book is available at *www.fda.gov/cder/ob/default.htm*.) When the FDA declares two or more drugs to be therapeutically equivalent in the Orange Book, most state laws either permit or require pharmacists to substitute a lower cost generic version of a drug for the innovator product. Consequently, a substitutable generic product, if priced lower than the innovator it copies, quickly erodes the market for the innovator.

The FDA only determines that two drugs are therapeutically equivalent if it finds that they are pharmaceutical equivalents and bioequivalent. For parenteral drugs, bioequivalence is normally not an issue. Pharmaceutical equivalence, however, is likely to be a problem for biosimilars. If the FDA does not find that the biosimilar product has the same active ingredient as the innovator it copies, it cannot find the two products to be pharmaceutical equivalents. Nevertheless, the FDA has not, at this point, decided whether biosimilars can ever be therapeutic equivalents to the innovators they copy (however, *see box, INN*).

After Omnitrope was approved, Sandoz stated publicly that it would seek a therapeutic equivalence rating for its drug. No further information is currently available on that request or FDA's response to it.

For biotechnology products, which tend to be injectable and carry a high price, the FDA determination of substitutability may not be as important as it would be for another pharmaceutical. This is because third party payers may be motivated to, and may have the ability to, induce physicians to prescribe a lower cost biosimilar product in place of the innovator. The extent to which substitution of biosimilars will occur remains to be seen. While the FDA's petition response attempted to suggest that there had been other approvals of follow-on protein products in the past, Omnitrope is the first true biosimilar approved in the US. Further, because there are already several human growth hormone products approved on the basis of full NDAs, the effect of the entry of the biosimilar may not be as significant to the market as would be the case where there was only one innovator.

INN

The FDA has addressed the substitutability of biosimilars in the context of a debate over whether separate International Non-Proprietary Names (INN) should be issued for biosimilar products. In a document entitled "US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (1 September 2006) the FDA said the following (among other things):

- With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.

- Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g. generation of a pathologic immune response.

At this time, the FDA acknowledges that biosimilars have not been demonstrated to be interchangeable through any scientific process.

IMPLICATIONS FOR APPROVALS OF OTHER BIOSIMILAR PRODUCTS IN THE US

In addition to the human growth hormone, the other significant biological product approved by the FDA under the FFDCA is human insulin. The FDA has stated it will issue guidance addressing what is required for approval of biosimilar versions of both human growth hormone and human insulin. Initially, it had suggested that it would have separate guidance for each. More recently, it has assured Congress that it intends to issue a general guidance that would cover both. Several states have filed a citizen petition with the FDA asking the FDA to issue that guidance, which they suggest has already been completed. The guidance has not yet been issued.

The FDA went to great lengths to suggest that the step it was taking in the Omnitrope approval was a limited one. Nevertheless, supporters of biosimilar approvals must be encouraged, and innovator companies must be concerned, that the Omnitrope approval, and the lack of any judicial challenge to the FDA action in that approval, may embolden the FDA to proceed with approvals of other biosimilars based on products approved under NDAs. Other human growth hormone products or human insulin products may be more likely to obtain approval. The existence of an unapproved application, if its sponsor does not choose to publicise it, is not public information. Therefore it is uncertain how soon other such biosimilars may obtain approval.

IMPLICATIONS FOR LEGISLATIVE CHANGE

Congressman Waxman and Senator Hatch were responsible for passing the Hatch-Waxman Act 1984, which facilitated approval of generic products under the FFDCA. Both have indicated an interest in exploring potential routes for approval of biosimilars approved under the PHSA, and on 29 September 2006 Congressman Waxman and Democratic colleagues in the US House and Senate introduced proposed legislation (H.R. 6257

and S. 4016) that serves to open the debate. That does not necessarily mean that this will become a legislative priority for either Congressman Waxman or Senator Hatch, or for any other legislators, in the near future. The Hatch-Waxman Act negotiations were notoriously difficult, and there is no consensus on how the scientific issues presented by biosimilars are best handled (or on whether approval of most biosimilars on less than a full data package makes sense at all).

On the other hand, the impetus to save money in healthcare, and in particular to save money on relatively expensive pharmaceuticals like biological products, is also a powerful force. A serious legislative consideration of whether there should be a route to approval of biosimilars will probably occur eventually.

The Hatch-Waxman Act contained significant protections for innovator products, including both periods of market exclusivity and patent linkage. Certainly, if a new legislative route for approval of biosimilars is considered, such protections for innovators will have to be on the table. The development of a new innovator biological product is both risky and capital intensive, and there would be caution about taking a step that would undercut the incentive to invest in such products.

The greatest significance of the Omnitrope approval, and of approvals of biosimilar products in Europe, may be in the fact that they put such products on the market. If, once marketed, the biosimilar products appear to be equally safe and effective as the innovators they copy, that will facilitate a legislative effort to develop a route to approval of biosimilar versions of biologics approved under the PHSA. This will likely be the effect even though it can be argued that, for other products, the issues and risks will be much more complex. If, on the other hand, there are safety or effectiveness issues with a marketed biosimilar product, that could set back any efforts to ease the approval process for such products considerably.

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