All eyes on Omnitrope

As the EU approves its first biosimilar therapy, a recombinant human growth hormone, Linda R Horton, Meredith Manning, Elisabethann Wright and Jaime Gallimore look at the implications for the European and US biotech markets

On April 18, 2006 Sandoz, the generics subsidiary of Novartis, issued a press release stating that the European Commission had granted a marketing authorisation for its product, Omnitrope (somatropin). This, the company declared, was the first authorisation of a "similar biological medicinal product" under the recently revised EU pharmaceutical marketing authorisation legislation. The Commission's decision has not yet been made public.

The news follows the positive opinion of the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) in late January 2006 on the Sandoz application. At the time, the EMEA press release indicated that authorisation would be of "a similar biological medicinal product". This opinion by the EU member states' most powerful assembly of drug regulators (one that carries more weight than a US FDA Advisory Committee vote) set the stage for the first European approval of a 'biosimilar' for human growth hormone.

Last month's approval of a so-called 'generic biologic' will have a substantial impact on the biotech marketplace in Europe. Moreover, as it now seems likely that a biosimilar will be successfully marketed in the EU, the FDA and US Congress could use the European experience as a basis for changing US legislation to permit follow-on protein (FOP) products – this is currently subject to a lawsuit involving the FDA.

Guidelines on biosimilars

Omnitrope references data and information contained in the marketing authorisation (MA) file for the reference product – Pfizer's human growth hormone treatment, Genotropin. The EU Community Code on Medicinal Products, which governs European MAs, allows approvals of generic products based on abridged applications. The expectation has been that applications for biosimilars must include substantially more detailed information than those for generic versions of small molecule drugs.

Indeed, this was made clear in various EMEA guidelines concerning biosimilar applications. These include a general guideline document, guidelines concerning clinical and non-clinical issues relating to the comparability of biotech-derived proteins as active substances, and guidelines concerning quality issues relating to the comparability of biotech-derived proteins as active substances. These guidelines offer the view that, because of the complexity of biologic/biotech-derived products, the small molecule generics approach is scientifically inappropriate for these therapies. The 'similar biological medicinal products' approach, based on a comparability exercise, would then have to be followed. Annexes add details on product categories, including one on human growth hormone (recombinant somatropin).

The role of the CHMP is to provide the European Commission (EC) with opinions on various types of applications – primarily whether the data and information accompanying the application are sufficient for the type of authorisation being sought. However, the opinion of the CHMP is not legally binding. Only the Commission has the power to make a binding authorisation decision, although it is required by law to provide a detailed explanation should it choose not to follow a CHMP opinion.

This was, in fact, Sandoz' second attempt to obtain EU approval for Omnitrope. It applied to the EMEA in 2001 to have the product considered for generic authorisation based on a detailed scientific bibliography, accompanied by certain studies aimed at showing comparability with Genotropin. In June 2003, the CHMP adopted a positive opinion on the application. But the EC subsequently chose not to follow that opinion. In March 2004, the EC published a notice in the Official Journal of the EU indicating its decision that the CHMP had improperly accepted the Sandoz application as a 'bibliographical application based on the well established use of the medicine', while at the same time it had accepted (and probably had required) comparability studies to be performed.

The 2004 decision is currently the subject of an appeal by Sandoz to the European Court of First Instance that is presumably now debatable. In the appeal, Sandoz contested the Commission's decision that the performance of comparability studies "implied that the legal conditions for the application of the [bibliographical application] procedure were not met."

Round two

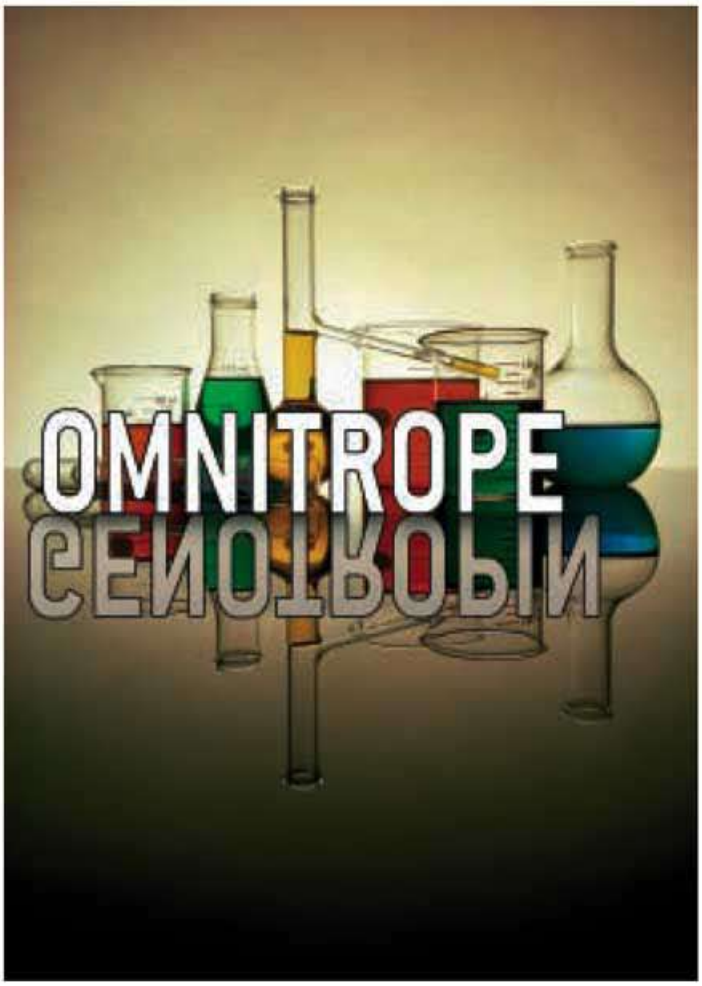
Sandoz submitted a second Omnitrope application to the EMEA in July 2004. This followed two amendments of the Community Code, one a Commission amendment to an Annex laying out the content requirements for MA applications, and the other a comprehensive overhaul by the Council and the Parliament that included a definition of 'similar biological medicinal product'. The second application was submitted not long after the date that the latter amendment became effective in the EU, but before the final date on which the EU member states had to adopt this provision in their national laws. Thus, the positive opinion in January 2006 was the CHMP's second on this product.

We do not know whether the second application, like the first, was an abridged generic application. However, on announcing its positive opinion, the EMEA's use of the phrase 'similar biological medicinal product' indicates that it considers the Sandoz product to be 'biosimilar' to Genotropin. The EMEA's January announcement included a footnote indicating that for 'similar biological medicinal products', it requires substantial additional data beyond what is necessary for generic products, particularly the toxicological and clinical profile. Thus, we can conclude that Sandoz has submitted, in addition to the data and information required for approval of a generic product, information designed to satisfy the relevant legal standard for a biosimilar.

The CHMP's second positive opinion on Omnitrope presents difficult issues. On the one hand, the statutory framework has been

strengthened by the addition of the amendments to the Community Code discussed above. At the same time, neither the new statutory framework nor the process preceding the second positive opinion may be sufficiently robust to withstand challenge. Consider the following points:

- In the second Omnitrope opinion, the EMEA disavowed use of the long-standing (and recently upgraded) generic process for 'essentially similar copies'. Furthermore, the relevant EMEA guidelines reflect the commonly-held view among leading regulatory bodies and the industry that, because of the complex nature of biologic products, it is not possible to create a follow-on of a biologic that is close enough to the reference product to be considered a true generic.
- At the same time, an argument can be made that the apparent legal basis for a biosimilar authorisation of Omnitrope is highly questionable. A key law cited by Sandoz as the basis for its application for authorisations is a piece of secondary legislation known as Directive 2003/63/EC, adopted in June 2003. It modified the European Parliament and Council's Community Code on Medicinal Products 2001/83. However, what the Parliament and Council empowered the Commission to do was to issue a modification to take account of scientific and technical progress, not to create entirely new types of MA out of whole cloth. (Translating this situation for US readers, we have a situation where a document similar to an FDA regulation may have gone beyond its Congressional authorisation.)
- The term 'similar biological medicinal product' is not defined. Oddly, it is referred to in the generics section of the revised Community Code but mostly to say that such a product is not a generic. The statutory language says more about the data required than what may safely be omitted.
- Furthermore, modification of the Community Code adding this provision on biosimilars was adopted in March 2004. It seems that Sandoz did the work for its July 2004 application (including preclinical or clinical trials relating to differences in raw materials or in manufacturing processes between Omnitrope and Genotropin) well in advance of the publication of this new statutory provision.
- The issue of the legality of implicit reliance on the innovator's trade secrets remains unresolved.



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The EMEA's various guidelines on similar biological products are also too recent to have guided the product development plan for Omnitrope. The notice of the Sandoz legal action suggests the company's 'comparability exercises' were based on the EMEA's adoption in 2001 of the International Conference on Harmonisation's (ICH) guidance on comparability as well as the review of the Omnitrope application itself. In fact, the ICH comparability guidance was meant to deal with 'intra-manufacturer comparability' not 'inter-manufacturer similarity'. In other words, this guidance was designed for situations in which a manufacturer's own product evolves (or where the follow-on product was derived from a precursor product whose cell line, production process, etc were acquired by the follow-on manufacturer). Thus, the ICH comparability guidance was designed only for cases in which the biosimilar is a linear descendant of the reference product. Accordingly, the one EU guidance document that could possibly have been in effect when Omnitrope was being developed was written for a very different, and much more limited, situation than the present one.

It is difficult to determine how far, if at all, Sandoz relied on the guidelines in submitting its second authorisation request. If its request was, like the original application, based largely on a detailed scientific bibliography plus studies carried out in accord with the ICH comparability guidance, Sandoz and CHMP members may have felt reliance on the newer guidelines to be unnecessary. If this is the case, the EU situation in the coming months may not be all that different from the situation at the time of the CHMP's first positive Omnitrope opinion.

Following announcement of the CHMP opinion, *BioCentury* reported that approved indications for the Sandoz product would be decided on an individual basis by the EU member states, as would substitutability for Genotropin and pricing. This press report apparently arose from a comment made by a representative of the generics industry. However, the notion that member states would have any say over approved indications is inconsistent with the fact that the Omnitrope authorisation is under the EU centralised authorisation procedure. All biotech drugs, including biosimilars, must be assessed by the EMEA, and for them, individual member states would lack the power to determine approved indications and interchangeability independently. Decisions about which products

are eligible for reimbursement, and about whether a physician or pharmacist may substitute Omnitrope for Genotropin are, however, matters for member states' national governments, not for the EU authorities. The comments quoted in the trade press may have been meant to refer to this traditional division of labour.

Follow-on proteins in the US

Meanwhile, a US judge has criticised the FDA for "egregious delay" in deciding whether to grant Sandoz' Omnitrope application. A series of key events and statements regarding FOPs set the stage for the controversy surrounding such products in the US. In April 1999, the FDA published a draft guidance stating that section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) could be used to gain approval of therapeutic protein products and that sponsors could make changes to a reference-listed drug if the change were supported by clinical data. In essence, by publishing the guidance, the FDA encouraged 'different' generics that rely on the safety and efficacy data of the innovator.

This prompted several objections from the innovator industry. The Biotechnology Industry Organization (BIO), for example, filed a citizen petition in April 2003 objecting to the use of this section to approve a biologic without a 'full complement' of non-clinical and clinical data. The FDA responded in October that year that its legal interpretation on 505(b)(2) applications was long-standing and it would resolve related scientific issues in the future. In April 2004, Genentech filed a citizen petition objecting to the FDA's use of innovator data in the review of the generic manufacturer's similar product, on the grounds that an agency reviewer must know details about the innovator's proprietary manufacturing process to determine whether the proposed follow-on is sufficiently 'the same as' or 'similar to' the innovator to support approval. In May 2004, Pfizer filed a similar citizen petition objecting to the approval of the Sandoz Omnitrope 505(b)(2) application, which in the US (as in the EU) involves reference to Pfizer's Genotropin.

The FDA held two public workshops in September 2004 and February 2005 to address scientific and technical (but not legal) issues related to FOPs. At the final workshop, acting deputy commissioner of operations, Janet Woodcock, said the agency would issue a background White Paper on its past regulatory and scientific treatment of protein products in the "next several months". It would then issue a set of draft guidance documents on different scientific issues for FOPs and hold a third public forum shortly thereafter. Then, public statements and action stopped and recently, the FDA said it would not issue a White Paper after all.

While EU regulators were considering the Sandoz Omnitrope application, a similar application had been under review at the FDA since July 2003. Sandoz filed a lawsuit against the agency last September for failure to take action on its pending 505(b)(2) Omnitrope application. In documents filed in the US district court in Washington DC, Sandoz said the FDA had notified the company on August 31, 2004, that its review division had determined it could not make an approval decision because of "unresolved scientific and legal issues." The FDA responded to the lawsuit asserting that it had not yet completed its review of the new drug application (NDA) or taken any final action, adding that "no timetable will be given by or for FDA to act on the Omnitrope NDA". Early this year, Sandoz filed a motion for summary judgment, and the agency's response defended the FDA's determination that it could not make a decision on the application. On April 10, 2006 Judge Ricardo M Urbina of the US District Court for the District of Colombia granted Sandoz' motion and ordered the FDA to make a decision on whether to approve the Omnitrope application.

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Until recently, the US Congress had been quiet on the issue of FOP legislation, but on February 10, Senator Orrin Hatch and Representative Henry Waxman wrote to the FDA urging it to issue guidance documents on the approval requirements for generic versions of insulin and human growth hormone. The letter stated that efforts to develop a regulatory framework for follow-on biologics approved under the Public Health Service Act (PHSA) "appears to be at a complete standstill," but that insulin and hGH should be separated from that debate in order that FOPs may be approved in those drug classes. Hatch and Waxman argued that, since insulin and hGH are regulated as drugs under the FDCA, the legal framework for generic approval already exists and they do not raise the same scientific issues because of their simple structures and long history of safe use. Of course, it is important to note that any such guidance would apply only to FOPs regulated under the FDCA, but the scientific principles would likely have an impact on the amount of data the FDA might require for the vast majority of FOPs which are regulated under the PHSA.

It remains to be seen whether the government will appeal the court order or whether the Congressional inquiry will jump-start the issue at the FDA. There have been no major statements about FOPs by acting commissioner Dr Andrew von Eschenbach or chief counsel Sheldon Bradshaw, and the agency has not ruled on the Genentech or Pfizer petitions. In addition, Waxman and Hatch's letter tacitly admits there is no consensus on Capitol Hill that legislation on FOPs will or should move forward in the near future. Thus, it seems clear that, without action by the FDA to move forward with approvals under the generic drug provisions of the FDCA, in response to the Sandoz court order or otherwise, there will be little action on FOPs in the US in the near future.

The ones to watch

While the US legal situation is being sorted out, EU regulators have taken the lead in attempting to define a policy and legal framework for biosimilars. But the EU statutory framework remains murky at best. The Commission's authorisation decision on Omnitrope will not have any direct impact on the FDA. Like the EMEA positive opinion, the Commission's decision could, however, give the FDA scientific cover for an approval of Omnitrope under section 505(b)(2) of the FDCA and may stimulate renewed Congressional interest in legislation. In the near term, however, the action is in courts in Washington DC and Luxembourg, where any legal challenge to the Commission's authorisation decision would be filed. Both venues should be watched closely.

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