nature biotechnology

The end of the beginning?

In late January, the European Medicines Agency (EMEA) finally reached a positive opinion on Omnitrope, the generic version of recombinant human growth hormone (hGH) developed by Sandoz, the generics arm of Novartis (Basel). The agency found that Omnitrope showed comparable quality, safety and efficacy to Genotropin, Pfizer's branded hGH. At the end of February, another Swiss biogenerics company, BioPartners, also received a positive opinion from the EMEA on Valtropin, a version of hGH developed with LG Life Sciences of Korea. Formal marketing authorization for both products now appears 'imminent.' Just before the Valtropin decision was released, the EMEA issued its final 'biosimilar' guidelines on nonclinical and clinical issues.

The media certainly got excited about the news; one breathless headline from the *Boston Globe* read: "European decision presages era of generic biology drugs." Elsewhere, the EMEA moves were heralded as opening a "path to cheaper biotech drugs" and a potential "billion dollar market for biogenerics." But if the era of biogenerics has begun—it appears to have started not with a bang but with a whimper.

It is certainly progress to have a clear regulatory path in Europe for copies of biopharmaceuticals (biogenerics or biosimilars), with two positive opinions on generic hGH products and applications for at least four other biogeneric products, including erythropoietin and interferon, in the works. But it is also clear that the regulatory path is much more winding and hazard-strewn than the shimmering, well-traveled highway for generic chemical entities. For the latter, the EMEA does not require manufacturers to undertake full clinical testing of their copied drugs. As with the US abbreviated new drug application, generic companies simply need to establish that their copy is comparable to a brand product using *in vitro* and *in vivo* bioequivalence tests. For biosimilars, on the other hand (at least if Omnitrope is anything to go by), the EMEA is going to require manufacturers to submit extensive clinical data—up to and sometimes including phase 3 data. Once they get approval, manufacturers will also be required to carry out extended pharmacovigilance.

At least the EMEA has done some streamlining of its data requirements for biosimilars. For instance, "routine toxicological studies, such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity" will not normally be required. However, in general, the concessions to biogeneric manufacturers seem cheese-paringly small. The burdens appear to have been hardly lifted at all with respect to clinical work: the guidelines state that "normally, comparative clinical trials are required for the demonstration of clinical comparability," raising the prospect of head-to-head clinical work involving the generic and market incumbent molecules. In other words, more clinical work may be required for approval of a generic version than for the original approval. Perhaps Sandoz should have bypassed the biogeneric route and presented Omnitrope as a new therapeutic entity using the regular marketing authorization process.

There are two perspectives into which the positive opinions on Omnitrope and Valtropin need to be placed.

The first is the sobering thought that hGH is one of the simplest, smallest and best-characterized recombinant proteins in medicine today. Although the EMEA has undoubtedly erred on the side of caution in considering the precedent-setting Omnitrope application, Sandoz had to jump through an awful lot of regulatory hoops to get approval. It seems very unlikely that the EMEA will lower the bar very much for purveyors of copies of more complex proteins, such as interferon or erythropoietin, or antibodies. Human growth hormone has no glycosylation sites and hence no possibility of being produced in differently glycosylated variants. Molecules such as erythropoietin and alpha interferon are glycosylated on multiple sites. A typical antibody molecule has over a thousand chiral centers, billions of enantiomers and extensive glycosylation as well as other post-translation modifications. Biogeneric versions will probably not show sufficient chemical and *in vitro* similarity to be exempted from a full testing requirement.

In this light, the business case for biogenerics is looking less attractive. Copying a brand protein not only requires an enormous reverse engineering effort (often with scant knowledge of the brand manufacturer's master cell line, fermentation method or purification procedure), but also experience and know-how in protein manufacture and process quality. If costly and large-scale clinical testing in humans is also required, launch costs are going to be high and it may be difficult significantly to undercut the price of brand products. Under the present regulatory regime, therefore, there is a very strong likelihood that copies of biopharmaceuticals in Europe will not be substantially cheaper than the original brand. Biogeneric manufacturers will, in essence, be marketing 'me-too' protein products at 'me-first' prices. And that is going to make it pretty difficult to dislodge the market incumbents.

Despite all these difficulties, at least Europe now has some competition in its biologics markets. This is decidedly not the case in the United States, allegedly the home of competition and the land of the free market. In America, biogenerics appear to be about as welcome as a cold sore on a first date. Despite assurances to Orrin Hatch (Republican-UT) in a Senate hearing in August 2004 that it would act on this issue, the US Food and Drug Administration has continued to tiptoe around (some might say drag its feet) on biogenerics regulation. A white paper on biogenerics promised in 2005 has never materialized. In the meantime, the top ten biotech companies—with their combined 84% share of the protein drug market—are essentially enjoying a second monopoly (to follow their patent monopoly) following expiry of their intellectual property. This is unacceptable. Even if biogenerics are not going to be the solution to the US healthcare system's financial woes, at least the American people should be given the opportunity to benefit from a greater choice of medicines.