Biogenerics: Europe takes another step forward while the FDA dives for cover

'…the European regulatory stage is set for an objective evaluation of similar biological medicinal products.'

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The term 'biogeneric' is usually taken to mean a therapeutically equivalent version of a currently marketed recombinant DNA-derived protein product that is manufactured by a company that is independent from that responsible for the 'originator' product. By definition, these products are not duplicates of the originator product because the structural heterogeneity that is introduced during the manufacturing process is considered to preclude the demonstration of 'essential similarity', at least in the terms that are applied to small molecules. Accordingly, the use of a conventional abridged regulatory dossier is inappropriate. Nevertheless, there are several precedents for the registration of 'comparable' biopharmaceutical products that do differ in their manufacturing processes, which has an impact on their physico-chemical and/or biological characteristics, but that are considered to have an acceptably similar clinical efficacy and safety profile. These include the various versions of granulocyte colony-stimulating factor (G-CSF), interferon-β, erythropoietin, insulin and human growth hormone (hGH).

The turning point for comparable biopharmaceutical products came in 1996 with the inception of the 'well-characterised biologics' philosophy of the FDA, which was accompanied by the introduction of 'comparability protocols', as a mechanism for minimising the regulatory burden that was associated with post-approval manufacturing changes. This irrevocably broke the 'process = product' dogma and enabled originator companies to minimise the costs of optimising their commercial manufacturing processes. By using a reduced clinical and non-clinical data package to demonstrate comparability, companies such as Amgen (http://www.amgen.com) and Biogen (http://www.biogen.com) were able to market versions of products that were different from the compound that was evaluated in pivotal clinical studies [e.g. Epogen™ (Amgen) and Avonex™ (Biogen)].

It could be argued that a paradigm shift of similar magnitude has occurred more recently with the FDA's refinement of a risk-based approach for the assessment of the impact of changes in manufacturing, and the transfer of responsibility for the jurisdiction of many biologics from the Centre for Biologics Evaluation and Research (CBER; http://www.fda.gov/cber) to the Centre for Drug Evaluation and Research (CDER; http://www.fda.gov/cder). Possibly, this reduction in regulatory complexity could facilitate the approval of therapeutically equivalent biologics. Ultimately, this would herald the advent of a regulatory foundation for the 'biogeneric dossier'.

Science versus political lobby

The debate concerning potential registration routes for biogeneric products has been most interesting in the way in which it has demonstrated the power, and success thus far, of the antagonists of this idea. As Robert Zeid [1] argued in a perceptive and searching article written several years ago, there is double-standard at large: the originators want their cake and they want to eat it for as long as they continue to grow fat, all the while remorselessly cranking the lobbying machine and constructing every type of smoke-screen to obscure the scientific debate. Tactics have ranged from the deposition of a succession of US Citizen Petitions to manipulating the International Conference on Harmonisation (ICH; http://www.ich.org) regulatory guidance drafting process to exclude consideration of biogenerics from the scope of the Q5E guidance on biopharmaceutical product comparability.

However, the regulatory tide is turning and in Europe substantial advances toward the establishment of regulatory procedures for biogenerics have been made. Surely, this will make it even harder for the FDA to acquiesce in front of the political lobby. Furthermore, as Karst has recently intimated [2], there are a number of compelling precedents that make resistance to biogeneric products increasingly untenable.

European position

As reported by Nicolas Rossignol (European Commission) at the Biogenerics symposium (29 May 2004, London, UK),

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which was sponsored by the European Generics Medicines Association (EGA; http://www.egagenerics), the European Union (EU) has now formally codified a regulatory pathway for 'similar biological medicinal products' in its Pharmaceutical Directive (2004/27/EC); this regulatory pathway has yet to be transposed into the legislation of individual Member States (deadline 30 October 2005).

Rossignol confirmed that a 'marketing authorisation' for a biological medicinal product that is deemed to be comparable to a previously authorised product could be submitted using the legal basis described in annex 1 (part II, section four or seven) of the Directive (2003/63/EC). The application would need to include data that justified differences from the reference product: the competent regulatory authority [in Europe this would be the Committee for Human Medicinal Products (CHMP)] will determine the exact data requirements according to the product and its proposed therapeutic use. Prevailing standards for the assessment of biopharmaceutical product comparability will form the scientific basis for the registration dossier of a similar biological medicinal product. Under specified circumstances, the 'mixed marketing authorisation application' (part bibliographic, part original data) route might be more appropriate. Because these products are recombinant cDNA-derived proteins, the Centralised Procedure (Regulation 726/2004) would be obligatory.

A new 'Bolar-type' provision will enable developmental studies to be undertaken within all EU Member States before the patent term of the reference product expires. A single 'Euro reference product' would be valid, even if the same product had not been registered in all Member States: national agencies would be expected to provide assessment reports for the reference product to the competent authority (CHMP) that is responsible for the review of the dossier for the similar biological medicinal product.

The European guidance on biopharmaceutical product comparability – last revised in December 2003 – had previously established the acceptability of the biogenerics scenario, in which a second manufacturer could avoid unnecessary repetition of specific non-clinical and clinical studies that had been performed for the reference product.

Another speaker at the Biogenerics symposium, Barbara van Zwieten-Boot (CHMP member for the Netherlands), explained that it might not be appropriate to develop detailed guidance on dossier requirements for specific products because this could restrict alternative scientifically valid approaches. The CHMP Scientific Advice Procedure might be the most effective method for the clarification of uncertainties before committing to a development programme; at least two companies have already pursued this approach for biogeneric products. Encouragingly, because surrogate clinical endpoints might offer more discriminatory parameters compared with standard clinical responses, there could be more latitude in the application of surrogate clinical endpoints in the comparability scenario than in the new product registration case. Hence, rather than representing a double-standard, this would acknowledge the ethical imperative to avoid conducting efficacy studies that would simply confirm what is already known.

Thus, the European regulatory stage is set for an objective evaluation of similar biological medicinal products.

North American position

Although the FDA has demonstrated highly effective leadership in creating a regulatory process for the demonstration of biologic product comparability, a pathway for the approval of biogenerics is still lacking. This apparent paradox is the result of several factors, with the two most important probably being the intellectual property scenario and the vigorous political lobbying by commercial stakeholders.

On the one hand, it might not prove easy to navigate the various product- and process-related patent restrictions. On the other hand, a sequence of Citizen Petitions that are addressed to the FDA, and are supported by active political lobbying, has sought to restrict the decision-making authority of the agency. However, the FDA's elegant and complete countering of the various arguments used to challenge its mandate to apply the 505(b)(2) approval route for products approved via the Food, Drug & Cosmetics Act (FDCA) is evidence that the contest has not been one-sided. The acceptance by the FDA in September 2003 of a hybrid dossier for a follow-on version of recombinant hGH [Omnitrop™; Sandoz (http://www.sandoz.com)] provides a strong test case; however, this is also the subject of a Citizen Petition.

Publication of much-awaited FDA guidelines on data requirements for the approval of follow-on biologics seems to have been further delayed by the intervention of the lobbyists – Janet Woodcock (FDA) recently stated that '…FDA no longer plans to issue a draft guidance on follow-on biologics this summer…' [3]. This is a pity, because the guidance documents have been ready for release since April 2004 and they reflect balanced views of highly experienced FDA experts. Thus, the comment made by Woodcock that the high-level of interest '…has caused us to have to broaden the scope and look further afield and so forth…' seems particularly lamentable.

Although the Biotechnology Industry Organisation (http://www.bio.org) has asserted [4] that the FDA does not have the authority for approving follow-on biologics under any of the legal statutes that it administers, there is seemingly nothing in the Public Health Service Act (PHSA) that

would prevent the FDA from considering a dossier that contained adequate quality and non-clinical and clinical data to demonstrate comparability between a reference and a follow-on product – providing that the assessment does not rely on a cross-reference to proprietary data. Thus, it might not be necessary to create additional legislation to enable the registration of biogenerics that sought comparability to any of the biologics that were originally approved by either CDER (FDCA) or CBER (PHSA). However, this point remains open for debate, particularly now that the authority of the FDA to affirm its scientific and regulatory convictions appears to have been undermined by the concerted activities of the commercial-interest lobby. Scientific reason notwithstanding, attempts to register biogenerics under the existing statutes would almost certainly be delayed by legal challenges. As a result, congressional directives could be the only feasible way forward. Indeed, this appears to be the most probable outcome following the congressional hearing held on 23 June 2004.

In Canada, the regulatory agency has previously declared its intent to consider applications for comparable biologics based on limited clinical data. The terms of the Food and Drug Regulations, which are enforced within the context of the Food and Drug Act, afford the competent authority considerable flexibility to reach its scientific conclusions on the adequacy of the data that support product and process differences. Accordingly, Health Canada was able to accept its first biogeneric dossier in 2003. It is worth noting that the statement of the regulatory position of Health Canada explicitly cross-references the FDA comparability guideline.

International position

Biopharmaceutical manufacturing standards in China, India, South-East Asia and South America are continuing to approach those established in Europe and North America. Locally manufactured versions of G-CSF and erythropoietin are available in some of these markets. During the next few years, considerable activity to commercialise these products into Europe and North America will probably be observed, possibly through the shipping of bulk drug substances into these regions for local product finishing and batch release.

The 'cost-of-goods' for these products will probably be in the same order of magnitude as the originator products, and the savings that can be achieved by virtue of potentially reduced clinical development and marketing costs remain to be demonstrated. Bearing in mind that many of these medicinal products are administered in a hospital environment, widespread marketing campaigns should not be necessary to achieve a viable market share, if prices can be reduced significantly to discount those of the originator products.

Second-generation biologics versus biogenerics

Originator products that have been modified with, for example, polyethyleneglycol (PEG) are already on the market (e.g. PEGylated or hyper-glycosylated versions of erythropoietin, interferons and G-CSF are available), and other post-translationally modified forms of first-generation biologics are under development. These second-generation products have enabled the established players to maintain, or even extend, their market share. This makes it even more difficult to accept that artificial barriers should be maintained to exclude competition from biogenerics once the product patent on the original product has expired.

However, it could be argued that the established players also have as much, if not more, to gain by supporting the pragmatic application of product comparability strategies. For example, it could be envisaged that the use of comparative studies, the design of which is informed by the established clinical efficacy and safety profile of a first-generation product, could lead to a reduction in the size of pivotal clinical study populations used to support the licensure of the second-generation biopharmaceutical products. Such comparative studies could be powered to demonstrate statistical equivalence of efficacy based on established biomarkers of efficacy and safety in a statistically valid manner without having to follow the standard regulatory requirements for novel molecular entities.

So, will we see the Emperor changing his clothes in a few years time?

Equitable standards?

Although the commercial-interest debate has focused on the 'full complement of data' notion as a standard of fair treatment, it could be argued that experiences with the original products might result in biogeneric products being assessed to higher standards. Certainly, regulatory expectations for bioanalytical methods to measure humoral immune responses to biologic products have increased, as evidenced by post-marketing commitments that have been imposed on different sponsor companies. Clinical observations of serious adverse drug reactions to products such as erythropoietin, along with the recognition that existing bioanalytical assays have not been standardised to enable valid inter-product comparisons of immunogenicity, are driving the bar upwards. Regulatory agencies – and the wider public interest they represent – will need both the originator and follow-on product manufacturers to disclose their data fully to enable the application of equitable standards.

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The subtext here is that sponsors of the originator products might have been less than open in their sharing of results and important data that could inform the risk-assessment for the benefit of the wider public interest, which is an objective that the same sponsors promote when it suits them – that is, to slow the introduction of biogenerics by seeking to 'broaden' the debate.

The coming year

Now that the European regulators have demonstrated an unequivocal intent to accept the concept of a reduced data package for similar biological medicinal products, there is a strong incentive for developers of biogeneric products to commit to the clinical studies that are necessary to support licensure in Europe – some probably already have clinical studies underway.

Perhaps a biogeneric will not make it onto the European market before 2006, but it is conceivable that a product will gain entry to the Canadian market before that time. For once, the USA is likely to be some way behind and it can only be hoped that Congress will once again enable the FDA to assert its authority in a scientifically meaningful way.

However, a bigger hope is that the upholders of the commercial-interest debate will realise that their resources would be more productively directed to the development of novel and second-generation biologic products, as opposed to applying disingenuous diversionary tactics that could limit their own opportunities to benefit from more scientifically-rational (and cost-effective) approaches to product registration. Will the delaying arguments of today rebound to haunt tomorrow?

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