Follow-on biological products: the regulatory minefield

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As healthcare costs around the world continue to rise, governments, faced with the challenge of managing and financing their healthcare provision, are increasingly devising cost saving measures. One such measure involves encouraging the development of the market for generic products. This is being achieved through administrative initiatives designed to increase the market penetration of generics (comprising of measures largely introduced by local health authorities aimed at increasing and promoting the prescription and substitution of generics). In addition, legislative initiatives and court decisions are eroding the ability of innovators to protect research data submitted to regulatory authorities to support incremental improvements to existing products.

Biological products (see box, What is a biological product?) are as susceptible to this interest in generic copying as other types of conventional pharmaceutical products containing chemically synthesised drug substances. A number of first-generation biotechnology products will come off patent or lose marketing exclusivity or data protection in the next five to ten years (TOPRA Regulatory Rapporteur, February 2004 issue (see www.topra.org)). The market value of such products is estimated in the region of US$1.7 billion dollars (about EUR1.4 billion), presenting an attractive business opportunity for those looking to develop generic products.

However, there are high costs associated with developing a biological product. In addition to high research and development costs, there are significant additional costs involved in the routine production of biological products. These costs are the result of both the complexity of the manufacturing process for these products and the increasing regulatory demand for tighter control over the manufacturing process to ensure continued product safety. As a result, generic manufacturers have been exploring various ways to maximise reliance on an innovator manufacturer’s non-clinical (animal) and clinical data or that published in the literature (including information derived from public assessment reports and pharmacopoeia monographs) to support, at least in part, regulatory filings for biogeneric product authorisations.

Differences between chemical drugs and biological products (for instance, in relation to the approach to control, testing and standardisation) have led to ongoing debate in both the EU and the US about the appropriate regulatory path for seeking authorisation of a generic biological product.

Against this background, this chapter considers recent legislative and regulatory developments regarding the approval of biogenerics in the EU and the US. For the purpose of this chapter, the terms generic biological products, follow-on biological products, biogenerics or similar biological products are used synonymously.

EU

Owing to difficulties involved in using the conventional approach to approval for generic biological products, EC law has recently undergone revision. This section sets out:

- The conventional approach to approval of generic pharmaceutical products.
- The changes to the law that are taking place in this area, and specifically:
  - recent revision of EC pharmaceutical legislation (see EU pharmaceutical legislation: an overview of the main changes, in this Handbook), which has established a specific regulatory pathway for approval of follow-on biological products;
  - “soft law” guidelines issued by the recently renamed European Medicines Agency (EMEA) and its advisory committee, which expand on the details regarding data requirements for approval of biogeneric products. These guidelines seek to provide further clarity on the standard of approval of such products; and
  - case law developments, such as the Sandoz case (T15/04 OJ C71/35, 20.3.2004) which has raised issues about the approval of similar biological products.

Conventional approach

European pharmaceutical law requires an applicant for a marketing authorisation to submit an extensive data package, including results of non-clinical toxicological studies in animals and clinical trials in humans in order to demonstrate safety and efficacy of the product under normal conditions of use (see box, Obtaining a marketing authorisation in the EU). However, exemptions do exist from the requirement to submit results of the applicant’s own non-clinical and clinical studies under Article 10, Directive 2001/83/EC. An application can be submitted on the basis of an exemption (generally called an “abridged” application):

- With the consent of the originator to cross-refer to existing data on file for an “essentially similar” product (Article 10(1)(a)(i), Directive 2001/83/EC).

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WHAT IS A BIOLOGICAL PRODUCT?

In comparison with other types of pharmaceutical products, biological products are structurally more complex and involve manufacturing processes that require tight control in order to ensure their safety, quality and efficacy.

Biological products, because of their sheer size, are orders of magnitude more complicated than small molecule drugs. This can be seen by a comparison of molecular weight, which can be used as a measure of the size of a given product. For example, aspirin (a well characterised chemical drug) has a molecular weight of 180.2, while factor VIII, a coagulation factor used for treating haemophiliacs, has a molecular weight in the region of 300,000.

In addition, biological products possess a complex structure that is more susceptible to the conditions of manufacturing. An apparently innocuous change to a process or a formulation for one product may have detrimental consequence. For instance, in the context of experience with a product containing recombinant erythropoietin, it has been reported that more patients using one version of the product developed pure red cell aplasia, a severe immunological response that results in a need for blood transfusions.

Finally, the product arising from the manufacturing process is often not a pure, homogenous mixture. Rather, various forms of these molecules are usually present in the final product. In the absence of supporting data, one cannot predict whether a newly identified product change will be important or not to the safety and biological activity of a biological product. As a result, the conventional approach to testing the finished product in terms of its pharmaceutical and pharmacokinetic characteristics may not be sufficient to assess fully the clinical safety and efficacy of a biogeneric product.

Biological products are legally defined in the EU and the US as follows:

**EU**

A biological medicinal product is defined to mean a product that contains a biological substance. A biological substance has two important characteristics:

- First, it is produced by or extracted from a biological source.
- Second, there is a need to use a combination of physico-chemical-biological testing, together with process control, to define its quality and characteristics. As a result, the definition draws a clear distinction between a biological product and a chemically synthesised product.


Vaccines, products derived from human blood and plasma, products manufactured using a biotechnology process as defined in Part A of Annex to Regulation 2309/93/EC, and advanced therapy (such as gene- and cell-based therapy medicinal products) are considered to be biological medicinal products.

For the purposes of the centralised marketing authorisation procedure (see box, Obtaining a marketing authorisation in the EU), a biotechnology medicinal product is one that is developed by means of one of the following biotechnological processes:

- Recombinant DNA technology.
- Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells.
- Hybridoma and monoclonal antibody methods.

(Part A, Annex 1, Council Regulation 2309/93/EC. This definition remains unchanged following the recent adoption of Regulation 726/2004/EC.)

Recombinant DNA technology essentially involves the cutting and rejoining of the host genome with an exogenous gene sequence, which contains the genetic information required to produce the desired protein under certain conditions. As a result, the definition is sufficiently broad to capture not only all types of recombinant proteins, but also gene-based therapeutics and prophylactics such as gene transfer medicinal products and DNA vaccines.

**United States**

A biological product is defined 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 is relatively broad, and includes not only blood products, vaccines, and antitoxins, but also many proteins and other products of biotechnology.
OBTAINING A MARKETING AUTHORISATION IN THE EU

Under current EC law, marketing authorisations can be granted by way of either:

- A national authorisation under the decentralised system (with a procedure for mutual recognition after the first authorisation is obtained).
- A centralised system under which a single authorisation is obtained authorising marketing throughout all member states of the EU.

Biological products fall within the scope of the Annex to Council Regulation 2309/93/EC (see box, What is a biological product?), and, as a result, must be assessed centrally by application to the recently renamed European Medicines Agency (EMEA) (see EU pharmaceutical legislation: an overview of the main changes, in this Handbook). Central assessment is required regardless of whether the product contains a new drug substance or is a follow-on copy of an authorised product. (While there are provisions in the new Regulation 726/2004/EC (see main text, EU: Recent revision of legislation) for national approval of copies of certain centrally approved products, it would appear that these do not apply to copies of products derived from biotechnology processes.)

- Where the drug substance has a well-established medicinal use with recognised efficacy and an acceptable level of safety; and there is systematic documentation of its use in the EU for not less than ten years (Article 10(1)(a)(iii), Directive 2001/83/EC (the published literature exemption)).
- Where the generic product has been demonstrated to be “essentially similar” to the originator’s product and the relevant data protection has expired (Article 10(1)(a)(iii), Directive 2001/83/EC). A generic manufacturer usually uses this last head of “essential similarity” to justify extrapolation of the originator’s non-clinical and clinical data to his product for the purpose of gaining approval from the regulatory authorities.

The judgment in the Generics UK case (C-368/96) sets out the criteria for assessing similarity between the originator’s product (the reference product) and the generic product. The European Court of Justice (ECJ) held that two products, when compared, are essentially similar if they satisfy three central criteria, namely that they:

- Have the same qualitative and quantitative composition with respect to the active drug substance.
- Have the same pharmaceutical form.
- Are bioequivalent.

However, the ECJ indicated that satisfying the three criteria is not sufficient if the relevant medicinal product differs significantly from the original product in relation to safety or efficacy, for example, as a result of the inclusion of a novel excipient or because of different impurity levels.

As a result of Generics UK, it appeared that a generic manufacturer could rely on an originator’s non-clinical (animal) and clinical data only if both the products were essentially similar and the data protection period had expired. This seemed to indicate that data for a related product which was not essentially similar, could be protected from cross-referral. However, this apparent protection has been eroded significantly by Novartis (C-106/01). In this case, the ECJ determined that related products, regardless of whether or not they are essentially similar, are not protected from cross-referral, even if the relevant data protection period has not expired.

As a result of Novartis, incremental research using the same active substance is not generally protected, and resulting products can immediately be copied without the consent of the innovator.

Recent revision of legislation

EC pharmaceutical legislation has been under review in recent years, culminating in the adoption of Directive 2004/27/EC (amending Directive), which amends Directive 2001/83/EC (see EU pharmaceutical legislation: an overview of the main changes, in this Handbook). Member states must implement the amendments by October 2005. In addition, a new regulation, Regulation 726/2004/EC, replaces the existing regulation governing the centralised procedure for marketing authorisations (Regulation 2309/93/EC).

The legislation replaces the concept of “essential similarity” (see above, Conventional approach) with that of a “generic medicinal product”. The latter term is defined using the first three criteria set out in the Generics UK case (C-368/96). A special provision is added relating to biological medicinal products. Where a biological medicinal product claims to be similar to a reference product, but “does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided” (Article 10(4), amending Directive). These results must be included to ensure that the requirements of safety and efficacy are met (Recital 15 to amending Directive).

The language of the amending Directive makes clear that an assessment of quality and bioequivalence may not be sufficient to assure the clinical safety and efficacy of a “similar biological medicinal product”. Such clinical parameters can only be established by appropriately designed non-clinical and clinical tests.

Annex I to Directive 2001/83/EC (as amended by Directive 2003/63/EC) also appears to recognise the limitations of in vitro testing of the end product, and of conventional bioequivalence studies in the case of biological medicinal products (see box, Authorisation of generic medicines: conventional approach). It states that the particulars supplied to register a copy biological product are not to be limited to the data package normally
AUTHORISATION OF GENERIC MEDICINES: CONVENTIONAL APPROACH

Under the conventional approach to authorisation of a generic medicine, a generic manufacturer must demonstrate that its product is pharmacologically equivalent to the originator’s product (that is, it has the same amount of the same active ingredient(s), administered in the same dosage form) and that its product is equivalent to the originator’s product in its:

- In vitro performance. This is a measurement of the amount of drug substance that is released from a finished pharmaceutical product into solution in laboratory testing. For some injectable products, it is simply a function of the amount of the drug substance in the finished product. For certain dosage forms, such as tablets, however, the in vitro rate of release of the active drug substance into a solution may be affected by the way the product is formulated.

- In vivo performance. This is measured in terms of the bioavailability of the product, that is, the rate and the extent of absorption of the active drug substance into the bloodstream after administration to test subjects (usually human subjects) in appropriately designed pharmacokinetic studies.

Testing is largely based on the finished product where the differences are amenable to physico-chemical characterisation. If the differences fall within accepted tolerance limits in terms of, for example, levels of impurities and release of the active drug substance from the dosage form, then a marketing authorisation is usually granted. If there is no significant difference between the generic product and the innovator’s product in terms of its in vitro and in vivo performance with respect to certain defined pharmacokinetic and pharmaceutical parameters, the pre-clinical and clinical data relating to the innovator’s product can be extrapolated to the assessment of the copy product. The two products will be treated as therapeutically equivalent and the generic product may be used interchangeably with the innovator’s product.

required for the approval of conventional pharmaceutical generic products. However, the amending Directive leaves a sufficiently wide margin of discretion to the regulatory authorities to determine the extent of the non-clinical and clinical testing required for follow-on biological products, taking into account the characteristics of each individual medicinal product.

Guidelines

The EMEA and its advisory committee, the Committee for Human Medicinal Products (CHMP) (formerly the Committee for Proprietary Medicinal Products), have developed technical guidelines, which, although not legally binding, must be taken into account by marketing authorisation applicants (Annex 1 to Directive 2001/83/EC). As a result, they are an important tool for interpreting the legal requirements for obtaining a marketing authorisation, and indeed, are generally characterised as “soft law” by the European Commission.

These guidelines note that the concept of essential similarity is difficult to apply in the context of grant of a marketing authorisation for products derived from a biotechnology process. This is because the criteria of demonstrating the chemical, pharmaceutical and biological equivalence of larger molecules, for example proteins, are not defined (Volume 2A of the Notice to Applicants (November 2002 revision)).

The CHMP has issued a number of other guidelines relevant to products derived from a biological source or a biotechnology process, which have now been incorporated into the Rules Governing Medicinal Products in the European Union Volume III. Most recently, the CHMP has adopted two guidelines concerning comparability of biotechnology-derived proteins as drug substances, one of which relates to quality aspects and the other of which relates to non-clinical (animal) and clinical aspects. (CHMP guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: quality aspects; CHMP guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues). These guidelines:

- recognise the special features of biological and biotechnology products make it technically difficult to determine the comparability (the exercise that will demonstrate that two products have a similar profile in terms of quality, safety and efficacy) or essential similarity between a generic biological product and its reference product. Because the scientific issue underpinning these difficulties seems to derive from the fact that all biological systems are inherently subject to alteration. As a result, differences in starting material and in the manufacturing process can bring about profound effects in terms of product safety and efficacy.

- seem to envisage that quality data alone may not be sufficient for a follow-on manufacturer to satisfy the test for “comparability” with the originator’s product (although they do not rule out the possibility of comparability being demonstrated for a biogeneric product without additional studies). In relation to the comparability exercise they note that, “the extent of pre-clinical and/or clinical bridging studies will depend on the nature of the drug substance and formulation, and the complexity of its molecular structure as well as the possible differences as compared to the reference product” (pages 8–9/11 of the guideline relating to quality aspects).

- emphasise that the “efficacy and safety of a medicinal product claimed to be similar has to be justified, or if necessary, demonstrated separately for each of the claimed indications” (page 9/11 of the guideline relating to non-clinical and clinical issues).

- require that immunogenicity studies be performed. This requirement reflects the heightened anxiety of the regulators following reports that certain biological products, following administration, elicit an immunogenic response in the body. It is said that immunogenicity is a sensitive parameter of the biological characteristics of a protein, because of the specificity of the immune system, which is capable of detecting small changes in structure of the molecule.
Consider that even if the efficacy is shown to be comparable, the product may display a different safety profile with respect to nature, seriousness, or incidence of adverse reactions. Data accrued from pre-authorisation studies in patients may be too small to identify these differences occurring at a low level. The focus seems to be placed on product monitoring during the post-marketing phase so as to allow re-assessment of the risk-benefit balance of the similar biological product.

**Case law developments**

While the new legislation and guidelines attempt to clarify the standard of approval required for similar biological medicinal products, it is unlikely that they will resolve all the issues that are likely to be raised. The issue of approval of “similar” biological products has already been the subject of regulatory litigation pending in the Court of First Instance (CFI) in a case commenced by Sandoz against the Commission (T15/04 O J C71/35, 20.3.2004).

Sandoz seemingly had submitted an abridged application for Omnitrop, a recombinant human growth hormone, under Article 10(1)(a)(ii) of Directive 2001/83/EC (the published literature exemption) (see above, Conventional approach). The dispute between Sandoz and the Commission is said to relate to the interpretation of the published literature exemption and Annex I to Directive 2001/83/EC, which sets out the requirements for the submission of an abridged application under this exemption. In particular, it appears to raise the issue of whether product comparability studies are acceptable in an application made under the published literature exemption.

There appears to be a tension between the scientific view taken by the CHMP, which provided an opinion favouring approval and the legal position taken by the Commission. The Commission seemingly does not consider that the published literature exemption should be used to file an abridged application for a product that claims to be “similar” to the originator’s product. As reported elsewhere (BioCentury, 29 March 2004), the Commission takes the view that the correct legal basis for an abridged application for biosimilars is the third head of exemption (Article 10(1)(a)(iii), Directive 2001/83/EC) (see above, Conventional approach) in conjunction with Part II, Section 4 of Annex I to Directive 2001/83/EC (which defines “similar biological medicinal product”).

It remains to be seen how the case will be decided.

**UNITED STATES**

In the US, there has not yet been an approval of a “generic” version of a biological product. There has, however, been considerable interest in this subject. Many take the position that the concept of a “generic” biological product is a misnomer, and instead use the term “follow-on” biological product. The issue is complicated by the fact that most, but not all, biological products are approved by the US Food and Drug Administration (FDA) under a statutory provision which differs to that applicable to non-biological drugs. It is one that does not include a procedure for approval of generic products. As a result, statutory mechanisms for approval of “generic” versions of drug products are applicable only to a few biological products.

This section sets out:

- The current legislation and authorisation procedures applicable to the approval of biological and generic products.
- Proposals for legislative reform to facilitate the approval of follow-on biological products.

**Current legislation and authorisation procedures**

Two US statutes apply to the regulation of biological products. The first, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq) (FFDCA), applies to all drugs and medical devices. The second, the Public Health Service Act (42 U.S.C. § 262) (PHSA) provides an approval process for products that meet the definition of “biological product”. FDA administers both statutes.

A product that meets the definition of a biological product (see box, What is a biological product?) will generally be approved under the PHSA (although such products are also either “drugs” or “medical devices” within the meaning of the FFDCA). Approval under the PHSA is by means of a biologics licence application (BLA). At present there is no procedure for approval of follow-on biological products under the PHSA.

The mechanism for approval of generic drugs is contained in the FFDCA (section 505(j), 21 U.S.C. § 355(j)). Approval under this mechanism, known as the abbreviated new drug application (ANDA), will only be granted if the generic version is the “same” as the innovator product in a number of respects, including a requirement that the generic have the “same” active ingredient as the innovator product. (This requirement presents particular problems for biological products, which are often difficult to characterise by chemical identity testing in order to make a finding of “sameness.”)

In addition to the ANDA, FDA has administratively developed a controversial alternative mechanism for generic-type drug products to be approved, based in part on data submitted by an innovator, even when they are not the “same” as the innovator product that forms the basis for the approval (this is known as a “505(b)(2) application”). This mechanism is controversial because the statutory provision upon which FDA relies (section 505(b)(2), FFDCA, 21 U.S.C. § 355(b)(2)), does not appear to give it the relevant authority to approve applications on this basis. The issue is currently in litigation (Pfizer Inc v FDA, No. 1:03CV02346; DDC, complaint filed 13 November 2003, litigation currently stayed).

**Proposals for legislative reform**

Under the present system, the biological industry has enjoyed indefinite data exclusivity for products approved under the PHS Act, as there is at present no procedure for approving generic biological products under this legislation. However, some in the US Congress have begun to advocate a change in the law to permit some type of approval of biogeneric products. While various mechanisms have been suggested for permitting such approvals (see, for instance, box, 505(b)(2) applications and...
The controversy over 505(b)(2) applications (see main text, United States: Current legislation and authorisation procedures), is relevant to the potential for generic versions of biological products in two respects:

- First, some products of biotechnology that share characteristics with biological products are not regulated under the Public Health Service Act (42 U.S.C. § 262) (PHSA) and instead have been approved under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq) (FFDCA). Examples are human growth hormone and human insulin. The US Food and Drug Administration (FDA) has recognised that the abbreviated new drug application (ANDA) is unlikely to be appropriate for generic versions of these drugs because additional clinical studies may be required to satisfy experts that the generic will have the same effect in use as the innovator product, and have apparently concluded that 505(b)(2) applications may be preferable. (It has been reported that at least one such 505(b)(2) application has already been filed.)

FDA has stated that it is developing guidance to facilitate the submission of 505(b)(2) applications for these types of products. However, Genentech, one of the manufacturers of human growth hormone in the US, has filed a citizen petition with FDA arguing that the latter should refrain from publishing a draft guidance document relating to human growth hormone, if that guidance relies in any way on Genentech’s trade secret and confidential information. (See Citizen Petition of Genentech, Docket No. 2004P-0171 (8 April 2004). See also Citizen Petition of Pfizer, Inc, Docket No. 2004P-023 (13 May 2004), which raises similar issues.)

- Second, FDA’s 505(b)(2) application policy is a potential administrative precedent for a possible change in the law to permit FDA to approve “generic” versions of biological products that were approved under the PHSA. Some have argued that FDA could simply do this administratively by approving the generic version under the FFDCA, even though the innovator was approved under the PHSA. Others have suggested that the statutory provisions for approval of biological products in the PHSA could themselves be interpreted to permit a procedure parallel to the 505(b)(2) application process.

Dr Galson of FDA’s Center for Drug Evaluation and Research recently stated his view that FDA cannot approve generic copies of drugs first approved under the PHSA, if the approval of the generic would require any reliance on data in the innovator application. While that appears to be an appropriate reading of the legislation, it is not one that is universally shared.

If the law were changed to allow FDA to approve generic versions of biological products, there would still be a potential legal challenge. Under the US Constitution, there cannot be a “taking” of property without appropriate compensation. The innovator data included in the BLA is intellectual property of some significant value. It could be argued that a change in the law to permit the taking of that valuable property from the innovator applicants (by allowing FDA to rely on the data to approve a competitor’s product) would be unconstitutional in the absence of compensation. The issues in such potential litigation are complicated and it is not possible to predict at this point how such litigation would end.

Despite the difficulties, the demand for an easier route to market for such generic products has intensified as important biological products have reached or neared patent expiration.

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