Biosimilars: what is happening in the EU, and is the US about to follow the EU's lead?

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The question whether "biosimilars" should be approved by relying on the data developed by the sponsors of the innovator biologics that they copy has been controversial in the EU and in the US. Since the adoption of the new European pharmaceutical law, the EU has moved forward to create a route for such approvals. The US is, at the time of writing, actively debating whether it will follow the EU's lead.

Against this background, this chapter examines the:

- EU biosimilar approval regime.
- Debate surrounding the naming of biosimilar products that may have some bearing on the substitution of biosimilars for the innovators' products they copy.
- Statutory construct that has complicated the biosimilar debate in the US.
- Legislative proposals currently being considered in the US Congress.

THE EU

European pharmaceutical law governing regulatory data protection and approval of generic products is principally contained in Directive 2001/83/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Directive), which has now been amended by Directive 2004/27/EC (Code for Human Medicines Second Amendment Directive). European pharmaceutical law requires an applicant for a marketing authorisation to submit an extensive data package about pharmaceutical testing and pre-clinical toxicological testing results and clinical trial data to show the safety, quality and efficacy of a medicinal product.

However, traditionally, European law provides exemptions from the requirement to submit results of the applicant's own pre-clinical and clinical studies if certain conditions are met. These exemptions have survived in the new pharmaceutical law and are now contained in Article 10 of the Code for Human Medicines Directive (as amended). An applicant can rely on these exemptions to submit an "abridged" application, and they are:

- Where consent has been given by the originator to cross-refer to existing data on file for a medicinal product possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form (*Article 10c, Code for Human Medicines Directive (as amended)*).
- Where the drug substance has been in well-established medicinal use within the Community for at least ten years with recognised efficacy and an acceptable level of safety in terms of the conditions set out Annex I to the Code for Human Medicines Directive (*Article 10a, Code for Human Medicines Directive (as amended)*) (the so-called bibliographic or published literature exemption).
- Where the copy product is a generic medicinal product of the originator's reference product. A generic medicinal product is defined as a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference product, and whose bioequivalence with the reference product has been demonstrated by appropriate bioavailability studies (*Article 10(2)(b), Code for Human Medicines Directive (as amended)*).

The definition of "generic medicinal product" is largely based on the first three criteria given by the European Court of Justice (ECJ) in the *Generics UK case* (*C-368/96*) for assessing "essential similarity" between the originator's reference product and the generic product under the old law. However, the definition of "generic medicinal product" found in the new law also states that different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance must be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy.

Further, the new law introduces the concept of "global marketing authorisation" in Article 6(1) of the Code for Human Medicines Directive (as amended). The concept reflects, to an extent, the *Novartis* decision (*C-106/01*) that incremental research about additional strengths, pharmaceutical forms, administration routes, presentations as well as any variations and extensions, is not data-protected. This is because all these marketing authorisations are considered as belonging to the same global marketing authorisation for the application of the data protection period.

In the new European pharmaceutical law, a special provision is added for biological medicinal products in Article 10(4) (*Code for Human Medicines Directive*). 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". Recital 15 of the Code for Human Medicines Second Amendment Directive explains that these results must be included to ensure that the requirements of safety and efficacy are met.

The language of the Code for Human Medicines Second Amendment Directive makes clear that an assessment of quality and bioequivalence will not be sufficient to assure the clinical safety and efficacy of a "similar biological medicinal product" (that is, a "biosimilar" product). Such clinical parameters can only be established by appropriately designed pre-clinical and clinical tests.

Annex I to the Code for Human Medicines Directive (as amended by Directive 2003/63/EC) also appears to recognise the limitations of in vitro testing of the finished product, and of conventional bioequivalence studies in the case of biological medicinal products. Annex I states that the particulars supplied to register a copy biological product are not to be limited to the data package normally 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 pre-clinical and clinical testing required for a biosimilar products, taking into account the characteristics of each individual medicinal product. In fact, the type and quantity of supplementary data are now largely contained in the technical guidelines developed by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA).

Guidelines

Guidelines in general are not legally binding. However, Annex I to the Code for Human Medicines Directive makes it clear that applicants must take account of the scientific guidelines in assembling the dossier for application for marketing authorisation. As a result, they are helpful in interpreting the legal requirements for obtaining an authorisation because such guidelines are characterised as "soft law" by the European Commission. The ECJ also considers that Community guidelines must be given some weight in the interpretation of Community law.

The CHMP/EMEA have developed guidelines relating to assessment of safety, quality and efficacy of biosimilar products. There are essentially three categories of such guidelines:

- **The over-arching guideline.** This introduces the concept of a biosimilar product, and sets out the broad principles for dealing with biosimilar products. In addition, it provides a "road map" to the existing guidelines for biological medicinal products.
- **General guidelines.** These set out the general guiding principles for assessing the quality, pre-clinical and clinical aspects of biosimilar products.
- **Product type specific guidelines.** These guidelines have been developed to address specific requirements for pre-clinical testing and clinical trials for demonstrating safety and efficacy on a product type specific basis.

The over-arching guideline states that an assessment of product comparability on the basis of quality alone between the biosimilar product and the originator's reference product would not be adequate to establish the safety and efficacy of the biosimilar product. It also recognises that biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. There is a spectrum of molecular complexity among the various products based on the way they are manufactured that may give rise to differences in product characteristics.

In general, the regulatory position is that there is a need to provide supplementary pre-clinical and clinical testing data to make clear the safety and efficacy of a biosimilar product. The nature and the extent of such data would be determined on a case-by-case basis, taking account of the product characteristics, the route of administration, the dosing regime and the target patient population.

The over-arching guideline sets out seven broad principles for assessing "biosimilarity":

- The standard generic approach based on bioequivalence with a reference medicinal product by appropriate bioavailability studies applies only to chemically derived products and is scientifically not appropriate for biological medicinal products.
- An assessment of "biosimilarity" is based on comparability studies about quality, safety and efficacy between the reference and the biosimilar products.
- There is a general recognition that biosimilarity may be more difficult to establish for certain biological products, such as those that are extracted from biological sources, because they are not open to product characterisation.
- The approach to establishing biosimilarity is highly dependent on the state of the art of analytical procedures, the manufacturing processes employed and clinical and regulatory experiences of the product class in question.
- The quality assessment must have regard to:
  - the requirements set out in Annex I to the Code for Human Medicines Directive (setting out the basic requirements for submitting an application for a marketing authorisation);
  - the recommendations provided in the relevant technical guidelines; and
  - the technical requirements described in the relevant monographs of the European Pharmacopoeia.
- It is emphasised that, by definition, biosimilar products are not generic medicinal products because it could be expected that there may be subtle differences between biosimilar products from different manufacturers and the reference products.

To address specific pre-clinical and clinical issues relating to specific product types or product classes, the CHMP has developed a number of guidelines attached as "annexes" to the General guidelines. At the time of writing, guidelines relating to the following product types have been developed or are in development:

- Recombinant erythropoietins.
- Recombinant granulocyte colony stimulating factors.
- Somatropin (recombinant growth hormone).
- Recombinant human insulin.
- Lower molecular weight heparins (pre-clinical issues).

It is common ground that the CHMP expects certain non-clinical pharmaco-toxicological studies and well-designed clinical trials to be carried out to clarify the safety and efficacy profile of a biosimilar product. In the case of somatropin, it is recommended that at least one adequately powered, randomised, parallel group designed clinical trial should be provided to demonstrate comparability in clinical efficacy between the biosimilar product and the originator's reference product. Clinical trials should be double blinded to avoid bias. In contrast, in the case of erythropoietins, the product-specific guideline requires at least two clinical trials to be conducted to establish clinical efficacy of the biosimilar product.

In addition, it is generally recognised that administration of a protein to human subjects may elicit an antibody response to the protein. One type of antibody response (commonly known as immunogenicity) is known to cause adverse events and decrease in clinical efficacy. It is now generally required that immunogenicity must be studied for all biosimilar products to assess whether the manufacturing process can increase such response as compared with the originator's reference product. A draft guideline has now been developed to provide guidance on immunogenicity assessment of biotechnology-derived therapeutic proteins. This guidance describes both the:

- Factors that may contribute to induction of immunogenicity.
- Approach to assessing immunogenicity in pre-clinical animal models, including developing and validating the assays for assessing immunogenicity.

International non-proprietary names (INNs)

It is now accepted in the EU that subtle differences between biosimilar products and the reference products may not be fully appreciated until greater experience in their use has been established. Therefore, greater emphasis is now placed on post-approval pharmacovigilance monitoring in the form of a risk management plan.

There has been much debate in the EU and at the level of the World Health Organisation (WHO) as to whether each biosimilar active ingredient should be assigned with a different INN to assist the process of pharmacovigilance because generic prescribing and dispensing is based on INNs. An INN is assigned to each new active substance by the WHO according to the nomenclature rules. The debate has stemmed from the fact that there is a general expectation that once the biosimilar product has been approved, there is a potential for it to be used interchangeably with the originator's reference product because generic prescribing is generally encouraged at the level of the member states. To apply the pharmacovigilance monitoring effectively so that information relating to the biosimilar product is specifically collected, then a distinct INN should be assigned to each biosimilar active substance to facilitate product traceability and identification.

The INN nomenclature system was initiated in 1950 by World Health Assembly resolution and came into operation in 1953. The system as it exists today identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognised. INNs are intended for use in:

- Pharmacopoeias.
- Labelling.
- Product information.
- Advertising and other promotional material.
- Drug regulation.
- Scientific literature.

INNs are also used as a basis for product names, for example, for generics. The aim of the INN system is to provide health professionals with a unique and universally available designated name to identify each active ingredient. To facilitate use of medicinal products based on non-proprietary names, the WHO indicates that the existence of an INN system is important for:

- Clear product identification.
- Safe prescription and dispensing of medicines to patients.
- Communication and exchange of information among health professionals and scientists worldwide.

In its review of INNs for biological and biotechnological substances, the WHO has acknowledged that the nomenclature of biological medicinal products is an area of increasing complexity. However, there are general policies for designating a distinct INN for certain classes of biological and biotechnological substances to differentiate pharmacologically or structurally related substances according to:

- The source of the starting materials.
- The underlying mode of action.
- The primary and secondary structure, particularly differences arising from substitutions in the amino acid sequence or allelic variations. A chemically modified protein is differentiated from its unmodified parent molecule by using an appropriate descriptor (for example, "peg-" is used as the prefix for describing a protein that has been chemically modified with polyethylene glycol.
- The post-translational modification, particularly in relation to potential differences in glycosylation profile arising from use of different production cell-lines, and different manufacturing process and control, for example, erythropoietins (follicle stimulating hormones).

With regard to the naming of glycoproteins, the WHO has already established a system in which a Greek alphabet letter is used to describe each pharmacologically related substance. In the case of erythropoietins, this group of biologically related compounds are identified with a common stem (-poetin) and a Greek alphabet letter is used to differentiate between compounds of the same amino acid sequence as human erythropoietin that vary in the glycosylation pattern, for example epoetin alfa, epoetin beta, epoetin gamma, and so on. INNs with different amino acid sequence are named using the "poetin" stem and a random prefix, for example darbepoetin alfa.

Community law makes clear that in describing the product characteristics of a medicinal product, it must have a name, which can be either (*Article 1(20), Code for Human Medicines Directive*):

- An invented name not liable to confusion.
- A common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder.

The common name will always be the INN, if one exists. Use of a common name will not be open to most of the biosimilar products because the use of a common name is generally reserved for a drug substance where assignment of an INN is deemed to be inappropriate. For packaging and leaflets there is no obligation to use an invented name and indeed, there is an obligation to include the INN or common name, where the invented name appears.

It is the authors' understanding that the WHO Nomenclature Committee had discussions with industry and regulators as to whether the current INN system should be revised to accommodate the regulatory issues surrounding product identification of biosimilar products. It appears that the WHO has not given a firm decision as to whether the current system should to be changed. Additionally, issues relating to pharmacovigilance monitoring, in WHO's view, are a matter for the regulatory authorities to decide. Despite the debate, neither the EMEA nor the European Commission has so far required biosimilar products already approved in the Community to apply for a different INN. However, all these products are required to have a distinct trade name to distinguish them from the originator's products.

Experience with approval of biosimilar products

Since the adoption of the new regulatory path for biosimilar products, a number of biosimilar products containing somatropin and epoetin alpha (a version of erythropoietins) have been authorised in the EU. One of the somatropin biosimilar products (Omnitrope) now approved by the European Commission was the subject of regulatory litigation pending in the Court of First Instance in a case commenced by Sandoz against the Commission (*T15/04*). This case turns on whether, procedurally, an applicant is permitted to submit an application on the basis of the public literature exemption for a copy biological product. In particular, it appears to raise the issue of whether product comparability studies are acceptable in an application made under the published literature exemption. Given Omnitrope is now authorised in the Community, the outcome of this case would be of little direct consequence on the applicant or other biosimilar manufacturers because most of the applications are submitted under the new regulatory path through Article 10(4) of the Code for Human Medicines Directive.

It is clear that all these products have been authorised on the basis of information consisting of pharmaceutical data, pre-clinical testing and clinical trials. Although the data package falls short of that ordinarily required for a full clinical development, consistent with the published guidelines, applicants have nevertheless been required to submit certain pre-clinical testing results and appropriately designed clinical trials to show the clinical risk/benefit balance of these products. In addition, all these products once authorised are subject to post-approval safety monitoring. Therefore, the European regulators have treated biosimilar products very differently from conventional generic pharmaceutical products.

THE US

In the US, the Food and Drug Administration (FDA) approves most biologic drugs under a different statute than that which applies to non-biologic drugs. It approves most biologics under the Public Health Service Act (PHSA). It approves non-biologic drugs (and a few biologic drugs as well) under the Federal Food, Drug, and Cosmetic Act (FFDCA).

To obtain approval of an innovator drug under the FFDCA, the sponsor submits a new drug application (NDA) to the FDA for its review. To obtain approval of generic versions of those drugs the sponsor submits abbreviated new drug applications (ANDAs) or, when the generic varies from the innovator in certain ways, so-called "505(b)(2) applications". The 505(b)(2) application relies on an FDA finding that the innovator product is safe and effective plus data, which may include clinical trials, submitted by the 505(b)(2) applicant. Innovator drugs are approved under the PHSA through FDA review and approval of a biologics licence application (BLA).

There is, at the time of writing, no abbreviated statutory mechanism in the PHSA analogous to an ANDA or 505(b)(2) application for FDA approval of a generic, or biosimilar, version of an innovator biologic product. The US Congress is considering whether to change the law to create an abbreviated statutory route to such approvals.

This section examines:

- What legal standards may be put into place by a new law to permit approval of biosimilars in the US.
- How the FDA may, based on past performance and statements, be expected to implement that law.

The pending Senate bill

There has been discussion for some time of a change in the PHSA to authorise an abbreviated approval process for biosimilar copies of approved biologic drugs in the US. On 27 June 2007, the Senate Health, Education, Labor and Pensions Committee reported a bill with bipartisan support that purports to be a compromise between the interests of those supporting biosimilar introduction and those concerned about preserving incentives for innovation with respect to biologics. The bill, called the Biologics Price Competition and Innovation Act (*S.1695*), has not drawn unqualified support from either the biosimilar (generic drug) industry or the innovator industry. At the time of writing, the bill has not been passed by the full Senate, nor has it been considered in the House of Representatives. Nevertheless, the provisions of this bill provide, at a minimum, some hints as to what a final US law may look like.

The bill deals with a number of controversial issues, including:

- How much data must be submitted to support approval of a biosimilar product, and who decides what types of data are necessary?
- Can a biosimilar product be found to be interchangeable with the innovator it copies?
- Should there be a period of non-patent exclusivity during which the FDA cannot approve a biosimilar copy of an innovator product and, if so, should that exclusivity extend to new indications for an approved product?
- Should the new law provide a mechanism, which exists in the FFDCA provisions for abbreviated applications for generic drugs, to resolve some or all patent disputes during the time in which the FDA is considering approval of the biosimilar product?

Each of these issues has been controversial, and it is to be expected that the final US legislation will vary, in at least some respects, from the Senate bill. Nevertheless, this bill, unlike other legislation previously introduced in the House and Senate, appears to represent an attempted compromise of the opposed interests, and so may be predictive of the final resolution of these issues by the US Congress. The following briefly describes what the bill would do.

What is a biosimilar? The bill defines biosimilar to mean:

- "(A) that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; and
- (B) there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product".

Requirements for approval. The bill provides that the biosimilar applicant must, presumptively, submit data derived from analytical studies, from animal studies, and from one or more clinical studies to support the safety and effectiveness of its product for one or more condition of use. The statute, however, permits the FDA to waive the requirement to submit any of the studies if it deems a waiver appropriate.

In addition, the biosimilar applicant must show that its product and the previously approved "reference product" on which it relies use the same mechanism(s) of action for the condition or conditions of use recommended in the proposed labelling. This requirement, however, applies only if the mechanism(s) of action of the reference product is known.

The biosimilar applicant must also submit information showing that the conditions of use in its proposed labelling have been approved for the reference product and information showing that the route of administration, dosage form, and strength of its product are the same as those of the reference product.

The applicant must also show that the facilities where its product will be manufactured meet appropriate standards.

The applicant can also choose to submit additional data.

Interchangeability. The biosimilar applicant can choose whether or not to seek an FDA finding that its product is "interchangeable" with the reference product. The bill defines "interchangeable" as meaning that the biosimilar product "may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product".

To find interchangeability, the FDA is required to find that the biosimilar can be "expected to produce the same clinical result as the reference product in any given patient". If the biosimilar will be administered more than once to an individual, the FDA must also find that there is no more risk from switching between the biosimilar and the reference product than there would be in using the reference product without switching.

The bill does not address specifically the question of whether a biosimilar product will have the same generic name as the reference product that it copies. However, in a provision relating to whether the applicant must perform paediatric studies of its product, the bill states that an interchangeable product will be considered to have the same active ingredient as the reference product, and so not be required to perform new paediatric studies, while a biosimilar product that is approved without a finding of interchangeability will be considered to have a different active ingredient, and so, presumably, would be required to perform paediatric studies or obtain a waiver of that requirement.

Whether this statutory statement that a non-interchangeable product would be considered to have a different active ingredient than the reference product it copies would mean that the active ingredient would be assigned a different name is unclear. In a somewhat related context, when the FDA approved a 505(b)(2) application for a version of a drug called "conjugated estrogens" that it believed could not be said to have the same active ingredient as the innovator, it required the second product to bear a distinct, though closely related, name, "synthetic conjugated estrogens, A".

As an incentive to biosimilar applicants to obtain an FDA finding of interchangeability, the bill provides a period of biosimilar exclusivity during which, after FDA has found one biosimilar product to be interchangeable, it cannot find another biosimilar product to be interchangeable with the same reference product. The length of the exclusivity period would vary depending on issues relating to patent litigation, but, in its simplest form, would provide one year during which a finding of interchangeability for another product would be delayed.

Exclusivity. The bill provides that no biosimilar application can be submitted until four years after approval of the innovator it identifies as a reference product. It provides that no biosimilar application can be approved until 12 years after the approval of the reference product. No exclusivity is granted for a supplementary application for a change to the reference product, such as a new indication. Some congressional leaders in the House of Representatives have stated publicly their view that 12 years of market exclusivity is too long, while other bills have included a 14-year period. Consequently, at the time of writing, the question of how long an exclusivity period will ultimately be granted remains in doubt.

Resolving patent litigation. The FFDCA includes a provision that has the effect of resolving many patent disputes during the time in which a generic product approval application (either an ANDA or 505(b)(2) application) is pending. Innovator companies are required to provide information to the FDA about patents covering the innovator product and its approved uses (though not process patents) and the FDA publishes that information. Approval of the generic product is then delayed until expiry of such "listed" patents, unless the generic applicant challenges the patents as invalid or not infringed by its product. If it does challenge the patents, the innovator can sue at the time of the challenge and can obtain a 30-month delay in the approval of the generic while the patent litigation goes forward.

This procedure for resolving patent issues during the approval process is considered to be a significant advantage for innovator companies because of the potential for a 30-month delay in approval of the generic product while patent litigation proceeds. The process also has advantages for generic companies, however. It allows them to avoid the sometimes uncomfortable position of marketing their products "at risk" of patent litigation, because the litigation is resolved while the generic product is going through the FDA review process.

The Senate biosimilars bill does not adopt the FFDCA patent resolution provisions. Instead, it includes a complicated process by which the reference product manufacturer and the biosimilar manufacturer exchange information concerning the biosimilar application and any relevant patents. It provides that some, but not necessarily all, pending patents can be litigated during the approval process. The patent exchange procedure is too complicated to describe here, but it is widely regarded as being favourable to the biosimilar applicants and not particularly friendly to innovator patent holders.

How would the FDA use a biosimilar approval procedure if the statute provides one?

In a statement on 2 May 2007 before the Subcommittee on Health of the House Committee on Energy and Commerce, Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer of the FDA, made it clear that, "because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product [biosimilar] could demonstrate that its product is identical to an already approved product". She then explained the FDA's views that an FDA finding that a follow-on protein product can be approved as safe and effective should be distinguished from a determination that that product would be substitutable and suggested that, in appropriate circumstances, the FDA would be able to approve a biosimilar product through an abbreviated pathway.

A significant question, addressed in the EU but not fully resolved in the US, is whether and in what circumstances there can be a scientific basis for approving biosimilar products. The fact that a few biologic drugs are, for historical reasons, approved under the FFDCA has given the FDA a chance to look at that question in a case in which there is not a statutory barrier to approval of a biosimilar.

The FDA approved a "follow-on" or biosimilar product under the FFDCA when it approved the Sandoz human growth product, Omnitrope, on 30 May 2006. For historical reasons, although they are biological protein products, human growth hormone products have been approved under the FFDCA rather than the PHSA. The FDA was therefore able to approve a 505(b)(2) application for the Omnitrope product, relying, in part, on data submitted by the sponsor of an innovator reference product, Pfizer's Genotropin.

The FDA delayed action on the Omnitrope application for some time, and ultimately Sandoz sued the FDA and obtained a court order requiring it to make a decision. The FDA then approved the product. At the same time, it responded to several citizen petitions that had been filed by those opposing the approval. In the response, the FDA explained that the approval had been based on:

- Clinical trials comparing Omnitrope to Genotropin.
- Trials using Omnitrope in paediatric patients.
- Pharmacology and toxicology data specific to Omnitrope.
- Pharmacokinetic, pharmacodynamic, and comparative bioavailability data comparing Omnitrope and Genotropin.
- Testing that demonstrated that the structure of the active ingredient in the two products was similar.

The FDA ultimately concluded that Omnitrope is "highly similar" to Genotropin. However, the FDA also made it quite clear in the petition responses that the Omnitrope approval did not, in its view, resolve a number of pending issues about biosimilars:

- **Interchangeability.** The FDA said that Sandoz had not asked for a therapeutic equivalence rating (an interchangeability finding) for its product. (Sandoz subsequently did ask, but to date the FDA has not made any such finding.)
- **Evaluation of protein products that have unknown or multiple active ingredients.** The FDA noted that Omnitrope has one active ingredient.
- **Evaluation of proteins with an unknown mechanism of action.** The FDA stated that somatropin's mechanism of action is understood.
- **Evaluation of proteins that are difficult to characterise.** The FDA said that the human growth hormone can be characterised using currently available technology.
- **Issues associated with glycosylation.** Human growth hormone products are not glycosylated.

The FDA experience with Omnitrope, including the length of time it took to review the application and the questions it emphasised it had not addressed, suggests that the FDA is likely to exhibit significant caution in its review of any biosimilar application that is submitted under a changed US law. Because the experience with approval of biosimilars in the EU will be more extensive than that in the US, the confidence with which the FDA reviews potential applications under any new statute, or applications for the few biosimilars that might be approved under the FFDCA, may well depend on the FDA's perception of the safety and effectiveness in practice of biosimilars approved and used in the EU.

THE FUTURE

Regulatory authorities in the EU and the US are facing similar scientific and regulatory issues as they consider whether and how to approve biosimilar products based, in part, on data developed by innovator biologic manufacturers. The process is complicated in the US by the fact that there is not, as yet, a procedural route for approval of biosimilars, with limited exceptions, in that country. That, however, may soon change.