Challenges in the analysis of biosimilars were discussed at a recent meeting. Joseph Chamberlain reports

New versions of innovator biopharmaceutical products present multiple challenges for manufacturers and regulatory agencies. By reference to typical manufacturing processes for small molecules and larger molecules such as proteins, Fotis Fotiou, of Johnson & Johnson, Horsham, Pennsylvania, explained why biosimilars need special treatment compared with generics.

The structure of a small molecule drug is typically straightforward and well defined and can be confirmed using traditional analytical methodology. Small molecule drugs are synthesised using chemical reactions and are manufactured in a series of reproducible and predictable reaction steps. Their quality can be assured because active ingredients and purities are relatively easy to determine, degradation products are easy to predict and identify, and by-products, residual solvents and raw material impurities can be predicted, with specific methods being easily developed for accurate quantitation.

Biopharmaceuticals are normally grown in specially engineered cells developed with special consideration to development of a host cell, establishment of a cell bank, protein production, purification, analysis, formulation, storage and handling. Each stage can influence the characteristics of the end product. For example, the exact DNA sequence and the type of host cell used will have a significant influence. Thuss biopharmaceuticals and their manufacturing processes are inherently complex and cannot be fully duplicated. Small changes in the manufacturing process can lead to safety and efficacy issues and discrepancies in the same can be challenging, concluded Dr Fotiou, adding the watchword: “The process is the product.”

Regulators and intellectual property
Christian Schneider from the Paul Ehrlich Institute, Germany, gave some much needed definitions involving biosimilars in a review of the European regulations. First, a generic medicinal product is defined as one that has the same qualitative and quantitative composition, has been manufactured in a series of reproducible and predictable reaction steps, and that can meet the conditions in this definition for a reference medicinal product.

Biotechnological medicinal products are individual products. A good example is to be found in the products described as human insulin. The Eli Lilly product is obtained by a process of unfolding and refolding the protein, whereas Novo Nordisk has a product that is secreted with the native folding in place.

The European Biosimilar Framework offers an overarching guideline on similar biological medicinal products which defines the principles. However, the concept of similarity is evolving with the key questions being how much we need to know and how much similarity we need. The current situation is that there is scope for biosimilar development: biosimilars currently licensed are still relatively small molecules, different expression systems are possible, and biosimilar frameworks for more complex products such as alpha-interferons are imminent.

Current thinking is that the active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, a medicinal product containing interferon α-2a claiming to be similar to another biological medicinal product should refer to a reference medicinal product containing as its active substance interferon α-2a. Therefore, a medicinal product containing interferon α-2b could not be considered as the reference medicinal product. The difference is only in a single amino acid, which suggests that a biosimilar must be identical on the amino acid level.

For historical reasons, most biologicals are approved under the Public Health Service Act, whereas biologics, as defined under the Federal Food, Drug, and Cosmetic Act. This means that most biologics require submission of a biosimilar licence application (BLA) and non-biologic drugs require submission of a new drug application (NDA). For innovator products, the differences are not substantial with regard to regulatory standards for approval. Despite differences in the statute’s terms, each requires evidence of safety and effectiveness (or potency for BLAs). The current debate in the US, as always, relates to patient safety, assessment of similarity and interchangeability and, more recently, data exclusivity and other intellectual property-related issues. The underlying issues, which are more to the fore in the US, are to balance the competing interests of public health or public interests against legitimate commercial interests.

At least three bills on biosimilars are before the US Congress. They have much in common but each also has its own important features. The Waxman Bill defines the pathways for approval, the Eschoo Bill puts forward standards for assessing biosimilarity, and the Kennedy Bill has some special definitions. This situation can be confusing and there is much to anticipate within the US development of thinking on biosimilarity, concluded Dr Tsang.

US approach
Lincoln Tsang, of Arnold & Porter LLP, London, pointed out that the approach taken in the US has crucial differences from the European approach. There is a statutory definition of a biological product as being a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings. The US Food and Drug Administration has powers to set regulations and has defined analogous products to include most products of biotechnology.

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Protecting intellectual property
The issue of intellectual property protection was reviewed by Nick Sutcliffe, from Mewburn Ellis LLP, Cambridge, who accepted the US definition of biosimilar as a follow-on biological medicinal product whose similarity to a reference medicinal product is established by comparability studies.

In considering whether a biological can come within the terms of an abbreviated regulatory procedure, the main issues are patent status and data exclusivity. A patent is granted by a government to allow an inventor a monopoly covering activities relating to an invention
in exchange for a full disclosure of the invention. By its nature, a patent is territorial and temporary. The application is filed at an early stage in drug development; it involves a long and uncertain process, taking in a detailed application document, and searches and examination by a patent office. Even if granted, it is open to challenge.

A biological product may be protected by multiple patents relating to the active substance, the formulation, the indication and the method of manufacture. These various patents may have different expiry dates. Patent claims define what is protected by patent and are particularly complex for biologicals, where the active agent may be difficult to define or is not a reproducible chemical entity. There are several avenues to defeat patent claims may not cover follow-on biologicals, patent protection is less certain for biologics than for small molecules, longer development times decrease the length of useful monopoly.

Data exclusivity needs to be considered when the reference product undergoes the full regulatory process and the innovator submits extensive supporting data. In the abridged biosimilar regulatory process reliance is placed on the innovator’s data. However, property rights lie with the owner of the submitted data. Data sharing used for approval of biosimilars for a limited period. In Europe data exclusivity for biologics is treated the same way as for small molecule pharmaceuticals. In the US, there is no equivalent process for abridged approval of biologics.

Other forms of intellectual property can be found in trade secrets, manufacturing processes, proprietary materials and cell lines. The intellectual landscape for biologics is distinct, concluded Mr Sutcliffe. Patent protection may be weakened by narrow claims, but data exclusivity is of increased importance.

Techniques for comparison
An obvious starting point for assessing biosimilarity is to compare biological activity. Joanne Cooper, of NDA Analytics, reviewed methods available for assessing biologics such as monoclonal antibodies, fusion proteins, recombinant proteins, growth factors and expression vectors. The methods include in vitro cell-based potency assays (cell-toxicity, receptor/drug binding) and in vivo/ex vivo potency assays (enzyme-linked immunosorbent spot assay).

Assays should be performed that reflect the mechanism of drug action, said Dr Cooper, describing a number of case studies. Unlike traditional assays for small molecules, it is necessary to design and implement bespoke biological assays for each new drug, she concluded.

Immunogenicity problems
When a protein is injected into a patient, there is the potential for an allergic reaction, said Robin Thorpe, of the National Institute for Biological Standards and Control, London. In some fortunate cases, such as for the granulocyte colony-stimulating factor, the protein is non-immunogenic. Mostly, however, one can expect immunogenicity followed by one of three scenarios: an alteration of the pharmacokinetics and pharmacodynamics of the therapeutic agent; neutralisation of biological response or the clinical consequences and significance of such immunogenicity range from benign to seriously life-threatening. Because of the complexity of proteins any subtle change in a product’s manufacturing process can have enormous implications for immunogenicity, but it is impossible to predict the incidence of unwanted immunogenicity, the characteristics of the immune response or the clinical consequences and significance of such immunogenicity. All these need to be assessed in appropriate studies.

The current position is that testing for unwanted immunogenicity is integral to product development for ensuring the clinical safety of a biopharmaceutical. Immunogenicity studies need to be carefully and prospectively designed to ensure all essential procedures are in place before commencement and are usually developed on a case-by-case basis, taking account of product, patients, and expected clinical parameters. Immunogenicity issues occur throughout the life cycle of a product. Assessment requires an optimal antibody testing strategy, validated methodologies and reference standards. Unwanted immunogenicity is the biggest challenge for the approval of biosimilars, claimed Dr Thorpe.

EMEA guidelines
The European Medicines Agency guideline on the comparability of biosimilars includes a section on physicochemical analysis of biopharmaceuticals, said Gerry Maxwell, of NDA Analytics. A physicochemical characterisation programme should include determination of the composition, physical properties and primary and higher order structures of the active substance of the similar biological medicinal product. Just as the biosynthetic process gives proteins a degree of structural heterogeneity, so the similar biological medicinal product can contain a mixture of post-translationally modified forms. Efforts should be made to investigate and identify these forms.

In certain situations, the analytical tools used for characterisation may not be capable of directly comparing the active substance in the similar biological medicinal product with that in the reference medicinal product. In these situations, the applicant should use suitable approaches to isolate representative active substance derived from the reference medicinal product to perform the comparative analysis at the active substance level. These approaches should be validated in post-translational modifications, may be acceptable, but must be justified, concluded Dr Maxwell.

Ontology map system
Biosimilars are remarkably complex molecules, difficult to design and manufacture, increasingly difficult to reproduce and yet still desirable therapeutics. To study comparability in such products, the researcher faces a multitude of features and must decide which to focus on.

Post-translational modifications (PTMs) can be important structural features of biopharmaceuticals that determine product safety and efficacy. More than 300 such modifications have been reported, said Daryl Fernandes, of Ludger, Abingdon, who has embarked on a sophisticated scheme to tackle the problem of comparability of biopharmaceutical PTMs. This system, named GTO-QbD (GTO stands for “graph theoretic, ontology”, ontology being the study of relationships), uses so-called “ontology maps” that organise and show the relationships between different types of information on the drug.

The scheme builds on the principles of quality by design (QbD) and considerations of design space and knowledge space with ideas borrowed from mathematical graph theory. Dr Fernandes showed how one can use critical path analysis of these ontology maps to determine the critical quality attributes (CQAs) for the medicinal product and select the analysis methods most suitable for measuring these CQAs. Ultimately the analysis leads to the appropriate choices of measurement to obtain the most meaningful comparisons, and perhaps just as importantly, the elimination of inappropriate comparisons. The system is elegant and overcomes many of the problems found with traditional implementations of QbD. A detailed case study on cetuximab glycosylation illustrated the utility of the approach.