

Biotechnology medicinal products: Back to basics

Author

Philippa A Whiteside, Director, REGEXBIO Limited, Berkshire, UK.

Keywords

Biologicals; Analytical method; Protein structure; Process and control; Potency/biological activity; Immunogenicity.

Abstract

This article provides a basic view of what defines biological medicinal products, often called biologicals, and how they differ from chemical products. In entering into this thought process, let us remember that proteins range in size from small amino acid chains up to macromolecules of hundreds of kilodaltons in size. In addition, in order to appreciate the science behind the regulations, an understanding of organic chemistry is necessary, and preferably knowledge of molecular cell biology and how proteins are created in cells via the DNA expression mechanisms. Although the details are inevitably complex and specialist as a result, we will look at some basic concepts pertinent to biologicals so that a regulatory generalist can be effective in dealing with such products.

What is a biological?

In the EU, a medicinal product is defined in Article 1 of Directive 2001/083/EC (consolidated)¹ as: "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis." Thus a medicinal product is defined by its action.

However the definition of a biological medicinal product appears in the Annex to Directive 2001/83/EC, published in Directive 2003/63/EC² as follows:

Section 3.2.1.1: A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products:

- Immunological medicinal products
- Medicinal products derived from human blood and human plasma as defined, respectively, in paragraphs (4) and (10) of Article 1
- Medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93³
- Advanced therapy medicinal products as defined in Part IV of this Annex.

In all cases, a biological medicinal product is defined by what it is, and usually by its source.

In the US, where the term is a 'biological product' or 'biologic', the legal definition is provided in 21 CFR 600 Biological Products General, Subpart A – General Provisions, Sec.600.3 Definitions:⁴ "(h) Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man."

In practice, as stated on the CBER website,⁵ "Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources – human, animal, or microorganism – and may be produced by biotechnology methods and other cutting-edge technologies..."

Again, the definition of the product by what it is rather than its mode of action is true.

Why are biologicals different?

A biological is a combination of the drug substance, its product-related impurities and process-related impurities (see ICH Q6B).⁶ In contrast to most drugs that are chemically synthesised and their structure is known, most biologicals are complex mixtures that are not easily identified or cannot be finitely characterised. An arsenal of analytical methods is required, looking at the different levels of protein structures in orthogonal ways. As in the Indian fable, where six blind men were asked to describe an elephant, but each was limited to touching only one part of the animal's anatomy, so each analytical method tells us one aspect of the protein's characteristics – together they provide the overall structure and characterisation.

It is not possible to define the impurity profile on the basis of the starting materials alone – cellular systems create impurities that are undefined. This has led to statements along the lines of 'the process defines the product', and provides the basic thought processes that have driven the acceptability (or not!) of post-approval changes to biological products, and ultimately the barriers to the biosimilar concept. It also drives the need to provide extensive information in the quality dossier on the process and control of starting materials, both in terms of quality and safety.

There is also the need to monitor potency/biological activity as this determines the functionality of the medicinal product. A potency bioassay needs to be developed, usually based on an animal model, but later using a cell-based assay where possible. Often a reference standard must be defined in parallel (where an international reference standard may not exist) and the unit of biological activity must be defined, and justified.

Although susceptible to microbial contamination, whether from the process or adventitiously, biological drug products are usually restricted to parenterals; as terminal sterilisation is not possible (biological products are generally heat sensitive), it is necessary to use aseptic principles in the earlier manufacturing steps. Stabilisation of biological drug products also has to take into account their sensitivity to variations in pH or even to shaking.

Nonclinical testing requires a modified approach to take into account the species specificity of biological products, and that the

choice of a relevant animal species model needs to be demonstrated. Not only may the biological product be of limited activity in animals, but its clearance may be modified by immune-mediated clearance mechanisms. Standard toxicology programmes are generally inappropriate and a prediction of immunogenicity is necessary, especially for immune-modulating products.

Clinical pharmacokinetics of biologicals differ from those of new chemical entities (NCEs). Distribution is impacted by the compartmentalisation of proteins by bilipid membranes and limited by the need for active transport mechanisms. Clearance mechanisms are different and may be impacted by glycosylation.

Most regulatory professionals are aware that immunogenicity is a key issue, particularly following the high profile case of TeGenero's immunomodulatory compound, TGN 1412, in 2006. The impact can be either neutralising through induction of antibodies after repeated administration or stimulating where the product is immunostimulating. There is a risk that immunogenicity can knock out endogenous function, as widely reported for the Eprex (epoetin alfa) cases of Pure Red Cell Aplasia. Therefore, clinical development strategies should take into account the limitation of the nonclinical studies, including toxicology studies, as well as the impact on clinical efficacy.

Closing words

Aspiring regulatory professionals (and the job descriptions they are looking at) often express the need for "biologics experience". Over my career of approaching twenty years now in the development of biological products from the quality perspective, I have often reflected on what the differences or flash-points are. As a result, and the important distinctions between the two products, I do not

consider myself a generalist and shy away from commenting on the development of normal new chemical entities. Biologicals have different emphases across the quality, safety and efficacy disciplines; especially relevant in quality testing, a much higher amount of data is required and a more conservative approach is necessary towards post-approval changes and comparability.

References

- 1 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm
- 2 Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf
- 3 Now republished as Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf
- 4 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.3>
- 5 <http://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/default.htm>
- 6 ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.
- 7 <http://courses.cs.vt.edu/~cs1104/Introduction/6.blind.men.html>

DON'T BE LEFT BEHIND!

Let LIQUENT help your organization navigate the complicated regulatory world.

LIQUENT, the Global Leaders in Regulatory Management, provide life-sciences organizations with a variety of regulatory products and services. Whether you need regulatory submission or tracking software, regulatory submission outsourcing, regulatory consulting or comprehensive desktop tools, LIQUENT can help.

Contact LIQUENT now to learn more about any of their flagship offerings:

- LIQUENT *InSight*[®] - Manage Registrations, Publish & View Regulatory Content
- LIQUENT *Direct* - Regulatory Outsourcing Services
- LIQUENT[®] *SmartDesk*[™] - Comprehensive Desktop Tools

LIQUENT

www.liquent.com

inquiry@liquent.com