Robin Thorpe, PhD, FRCPath, UK

- Former Head of Biotherapeutics Group, National Institute for Biological Standards and Control, UK

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Biosimilar regulatory development in the EU – a stepwise approach

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Robin Thorpe, PhD, FRCPath
Email: rt7184@gmail.com

Biologicals – Definition

A biopharmaceutical, also known as a biologic medical product or more simply as a biologic or biological, is any medicinal product manufactured in or extracted from biological sources. Biopharmaceuticals are distinct from chemically synthesized pharmaceutical products.

Examples of biopharmaceuticals include vaccines, blood products or components, allergens, somatic cells, gene therapies, tissues, recombinant DNA products and living cells.

Biosimilars – EMA Legal Basis

A company may choose to develop a biological medicinal product claimed to be “similar” to a reference medicinal product, which has been granted a marketing authorisation in the European Economic Area (EEA) on the basis of a complete dossier in accordance with the provisions of Article 8 of irective 2001/83/EC, as amended.

Biosimilars – EMA Definition

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

Biosimilars in the EU

Biosimilars are now firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval, which allows marketing of safe and efficacious biosimilar products.

Biosimilars as Biologicals

- As is clear from the EMA definition, Biosimilars are Biologicals. They differ from innovator Biologicals in the regulatory process used for their approval.
- As Biosimilars are ‘scientifically’ Biologicals they should be regarded as such when safety and potency is being considered.
- There is no reason to treat approved Biosimilars any differently from all Biologicals (including innovator products).

Biosimilars – Comparability

Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the similar biological medicinal product and the chosen reference medicinal product authorised in the EEA.

Biosimilars – Development

A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical *in vitro* data.

Biosimilars – Stepwise Approach

1) Full quality (CMC) characterization of new product-to show suitability as a clinical grade product.

2) Comparative quality assessment of new product with reference product- to show comparability (biosimilarity).

3) Preclinical assessment.

4) Clinical assessment.

Principles of establishing biosimilarity

The ultimate goal of the biosimilar comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, conduct, endpoints and/or population to detect such differences.

Principles of establishing biosimilarity

A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed differences have to be duly justified with regard to their potential impact on safety and efficacy.

Biosimilars: Quality

Although quality aspects of a similar biological medicinal product are a fundamental element in the comparability exercise versus the reference medicinal product, quality aspects should always be considered with regard to any implications for safety and efficacy.

A stepwise approach should be undertaken to justify any differences in the quality attributes of the similar biological medicinal product versus the reference medicinal product in order to make a satisfactory justification of the potential implications with regard to the safety and efficacy of the product.

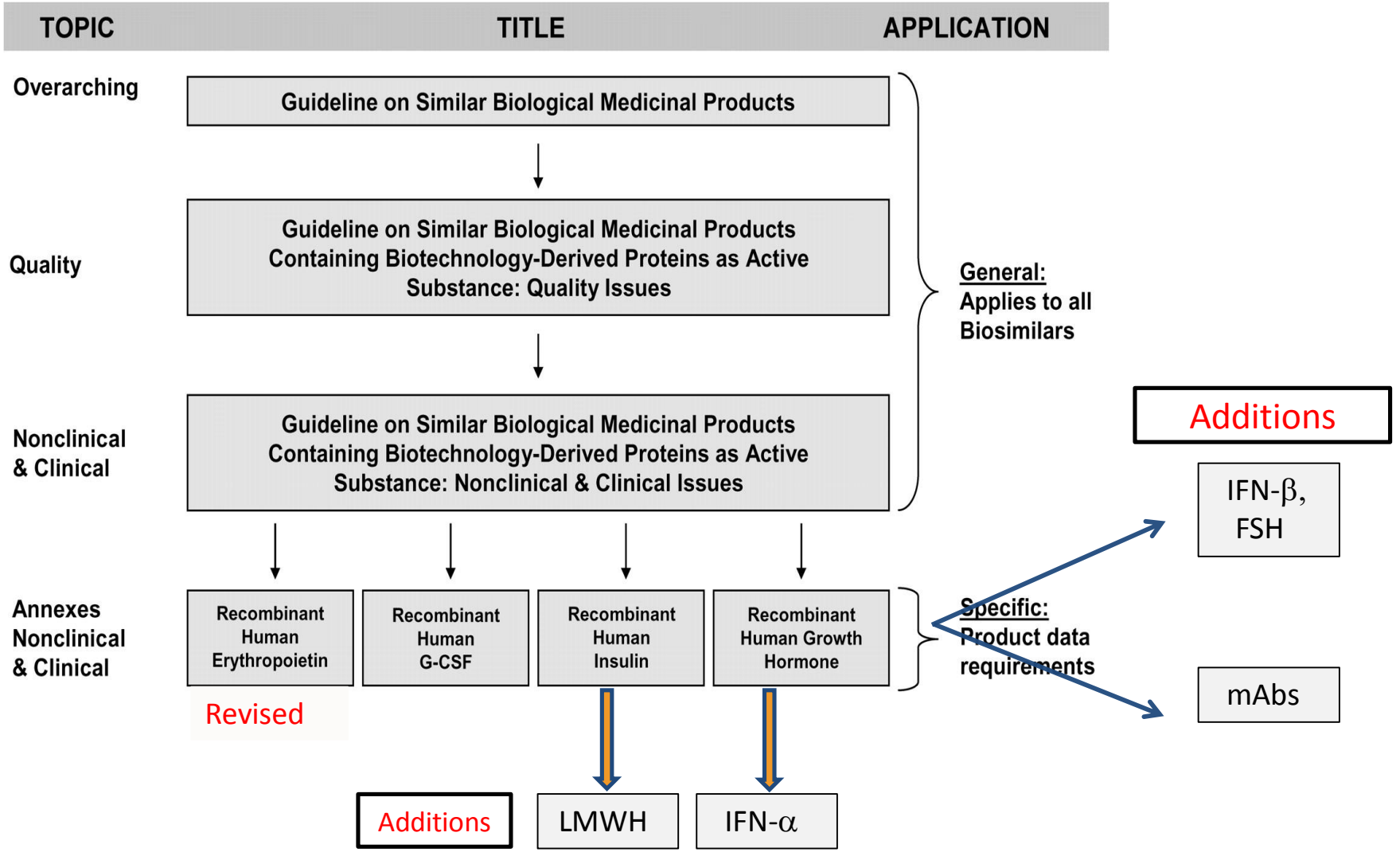
Biosimilar Clinical Guideline

The clinical comparability exercise is normally a stepwise procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical comparability.

Biosimilar Clinical Guideline-Efficacy

Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy per se, since this has already been established with the reference product. The sole purpose of the efficacy trials is to investigate whether a clinically significant difference between the reference and biosimilar products can be detected.

EMA Guidelines on Biosimilars



European Medicines Agency http://www.ema.europa.eu/, accessed 23 February 2011.

Uses of the Reference Product

The reference product is key and fundamental in the development of SBPs (biosimilars).

It is the ‘comparator’ for all the comparability studies i.e. for quality, nonclinical and clinical assessment.

It is ideally a product that has been approved and marketed in the relevant country or geographical area, which has a long established history of good efficacy and safety.

Uses of the Reference Product

It should be marketed at a level which allows the purchase of a number of different batches, so that the comparability assessment can be sufficiently thorough.

This implies that the most likely reference product for use as a comparator in SBP development will be the market leader in the country where the SBP is being developed, although this is not a requirement.

Biosimilars outside the EU

Outside the EU, several countries have adopted an identical or similar regulatory approach to the EU for approval of biosimilars, e.g. Australia, Canada, Japan.

But, this is not the case for all countries. Several have different approaches, inconsistent approaches or no approach at all for biosimilars.

Are all Biosimilars really Biosimilars?

- Terms ‘Biosimilars’, ‘Similar Biological Products’ & ‘Non-Innovator Products’ etc often used interchangeably. Can be incorrect.
- Non-Innovator Products or ‘Me-to’ products usually have not been evaluated using comprehensive comparability studies as required by EU and WHO guidelines. They are not biosimilars and should not be called biosimilars.

Quality of Products

The quality of products varies worldwide.

Some are very good. Others are not.

Batch to batch consistency also can vary.

Some products called ‘biosimilars’ in some countries are of inferior quality. But are they ‘real’ biosimilars?

The quality of biosimilars approved in the EU is high – like innovator products.

Conclusions

- The lead taken by the EMA in providing a suitable regulatory process for the evaluation and approval of biosimilars has ensured that biosimilar approval is feasible and that approved biosimilars in the EU are of appropriate quality.
- Biosimilars approved in the EU are evaluated according to criteria set out in a range of guidelines, which ensures the necessary safety and efficacy.