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Introduction to a global view of biologicals, biosimilars and non-originator (non-comparable) biologicals and selection of reference products

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GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

HACETTEPE UNIVERSITY
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Biologicals – Definition

A biopharmaceutical, also known as a biological 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 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: Comparability concept

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

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 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 and WHO

WHO has produced a guideline for evaluation of 'similar biotherapeutic products' (effectively biosimilars) which proposes a very similar approach to that described in the EU guidelines.

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.

Reference Products and Standards

Reference Products and International Standards/Reference Reagents:

Appropriate and Inappropriate uses in Biosimilar product development

Biosimilars – reference products and reference standards

Both reference products and WHO International standards/reference reagents have distinct and important roles to play in the development and characterization of similar biological products.

It is important to understand that these roles are distinct.

Their uses are not interchangeable.

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: Quality

Comparison can be made against 'official' data, e.g. pharmacopoeial monographs or against other published scientific data. However, such comparisons are limited and not sufficient to establish all aspects pertinent to the evaluation of biosimilarity.

Consequently, an extensive comparability exercise will be required to demonstrate that the similar biological medicinal product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product.

Biosimilars: Limitations

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 alfa-2a manufactured by Company X claiming to be similar to another biological medicinal product should refer to a reference medicinal product containing as its active substance interferon alfa-2a. Therefore, a medicinal product containing interferon alfa-2b could not be considered as the reference medicinal product.

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.

Biosimilars: Characterization

Extensive state-of-the-art characterisation studies should be applied to the similar biological and reference medicinal products in parallel to demonstrate with a high level of assurance that the quality of the similar biological medicinal product is comparable to the reference medicinal product.

Uses of WHO International Standards/Reference Reagents

WHO International Standards/Reference Reagents are primary standards (sometimes referred to as 'gold' standards) and are available for a wide range of substances.

They are produced to defined standards which optimize retention of biological activity and other important characteristics as well as ensuring stability.

Uses of WHO International Standards/Reference Reagents

They are often primarily intended for the calibration, characterization and validation of potency assays, often bioassays.

The standards can in some cases also be used with other assays and procedures.

They often contain excipients which may interfere with physico-chemical methods.

Uses of WHO International Standards/Reference Reagents

Such standards are usually calibrated in units or International Units which are often arbitrarily defined and relate to the ampoule content of the analyte.

These standards are used to calibrate bioassays either directly or for calibration of secondary or working standards

Biosimilars – Reference Products & Standards; How are they used?

For the development of biosimilars, the use of a reference product for the comparability studies is essential. There has been some discussion on providing 'standard' reference products which can be used for in the development of biosimilars, but this is not feasible as the reference product must be a commercial clinical product with an established clinical record. Reference products cannot be used as 'standards' for calibration of assays.

In contrast, WHO international standards and reference reagents are used for calibrating procedures, particularly bioassays.

They are not clinical products, and therefore cannot be used as comparators during biosimilar development.

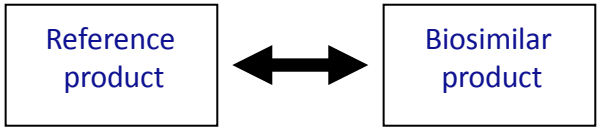
Implications of this for Biosimilar Development

The reference product and the international standard are 'very different things'.

- the reference product serves to define the quality criteria that the candidate must meet, a function that the reference standard does not serve

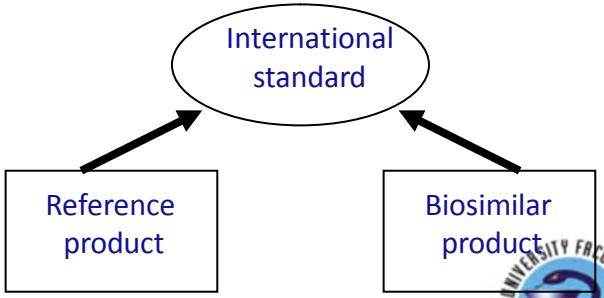
- the international standard serves to define and calibrate the performance of the test measurement system, a function that the reference product cannot serve

When you are trying to do this



What you actually do

Is this



Courtesy of Dr Adrian Bristow (modified)

Conclusions (1)

Reference products are approved clinical products usually obtained in the containers in which they are marketed. They are used as the comparator in comparability studies.

They normally have a nominal content of biological activity, with specifications around this for acceptance.

They do not have a single defined value of biological activity. There is no way of knowing what exact value this activity is, only that it is within the acceptance limits for the potency.

This implies that they cannot be used to calibrate assays.

Conclusions (2)

Reference standards, such as WHO International Standards have a defined unitage and so they are ideally suited for the calibration of assays.

WHO International Standards/Reference Reagents are not clinical products, even though the active substance in them may be derived from a product that was produced at clinical grade. They do not have any history of clinical use.

Therefore, these reagents are clearly inappropriate for use as comparators for biosimilar product development and should not be used for such purposes.