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A Review on Biosimilars Regulations in EU

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Abstract:

Since many popular biologic treatments are losing their patent protection, the biopharmaceutical sector has seen a notable increase in interest throughout the past 10 years. Biosimilar products are approved for commercialization by the regulatory body as well. Biological medications are pharmaceuticals created by biotechnology that have huge, complex molecules that are extremely sensitive to the parameters and conditions of manufacture. Because there is a higher chance of an immunological reaction, even a small alteration in the manufacturing process can affect the final product's quality and safety. For the purpose of developing new drugs, biopharmaceutical businesses use information technology, including statistical data and molecular modelling. Biosimilar medications are appealing since their marketing costs are moderate and typically 40–50% lower than those of original pharmaceutical products. Another name for biosimilars is "follow on biologics" or “similar biologics”. The following points needs consideration such as global harmonization, extrapolation studies, interchangeability study, long term post marketing studies to gain physician confidence in biosimilars.

Key words: AAM, INN, FDA, EMA, CHMP, PRAC.

Introduction:

Biosimilars, also known as follow-on biologics, similar biologics, or follow-on protein products, are biological products produced after the innovator biologics' patent expires. These biologics are suggested to have the same mechanism of action for ailments that are similar to those treated by the innovator biologic. Because there is no way for two biological products to be exactly the same due to the complexity of their production process and approach, the term "bio-generic" is ambiguous. Therefore, "Follow-on biologics" and "biosimilars" are frequently used phrases to describe such products. Since biosimilars are not classified as "generic medicines," several features related to the authorization procedure are not relevant. Aside from the specialized knowledge needed to identify the appropriate cell clone producing the protein, the process of manufacturing biosimilars is extremely difficult and costly. It's possible that not all significant structural and functional changes between two protein products can be found with the current analytical methodology. Furthermore, the connection between a product's structural characteristics and therapeutic performance might not be well understood. Because the products derived from biotechnology are complex, bioavailability and bioequivalence studies by themselves cannot conclude that there is bio-similarity. Instead, data from analytical studies, animal studies, and clinical studies are needed to demonstrate bio-similarity.

Difference between generics and biosimilar

	Biosimilars	Generic Drugs
Synthesis	Produced in living systems, generally using recombinant DNA technology	Produced through standard chemical synthesis
Identity with reference product	Designed and engineered to be similar, but cannot be 100% identical	Typically identical to the reference product
Structural features	Many layers of structure including primary, secondary, tertiary, quaternary, as well as post-translational modification	Typically simple molecular structure
Stability	Monitoring of manufacturing conditions required to maintain stability	Typically stable molecules
Immunogenicity	Immunologic testing and pharmacovigilance used to monitor for immunogenicity	Typically nonimmunogenic
Interchangeability	*Guidance pending* May or may not be interchangeable with the reference product – pending limitations on existing scientific methodologies	Interchangeable with the reference product, assuming similar purity and bioequivalence has been demonstrated
Automatic substitution	*Guidance pending* May or may not necessarily be automatically substituted with the reference product	Generally automatic substitution for the reference product is allowed
Nomenclature	International naming system for biosimilars is varied, US regulations for biosimilar naming are under development	Generally has the same INN as the reference product

Abbreviation: INN, International Nonproprietary Name.

Biosimilars council and AAM

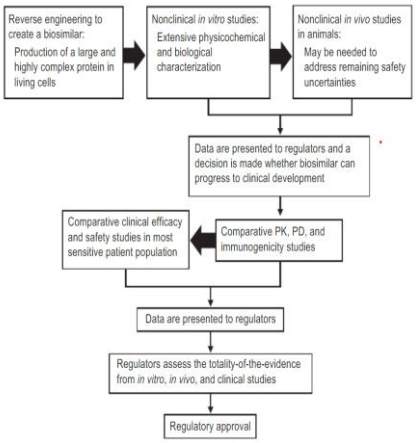
- The Association for Accessible Medicines (AAM) division, the Biosimilars Council, strives to create a favourable atmosphere for patient access to biosimilar medications.

- One of the best places to find out about the effectiveness and safety of less expensive substitutes for more expensive brand biologic medications is the Biosimilars Council. Expert education in public and health, strategic alliances, government relations, legal affairs, and regulatory policy are among the areas of emphasis.
- AAM is founded on the idea that everyone's life and the world around them may be profoundly affected by having access to secure, high-quality, and effective medical care. People's lives are improved by generic and biosimilar medications, which benefits society and the economy as a whole.
- AAM represents suppliers of various goods and services to the generic industry as well as producers and distributors of bulk pharmaceutical chemicals, biosimilars, and completed generic pharmaceuticals. In the United States, 90% of prescriptions are filled with generic medications, while only 23% of all drug expenditures go toward these medications.

Biosimilar development process:

The process of producing a biosimilar is very similar to that of producing its reference biologic; before biosimilars are released for distribution to patients, the EU requires that they exhibit no clinically meaningful differences and that they satisfy a strict scientific standard of similarity. This process is known as similarity testing, and it is used to verify that there are no clinically meaningful differences between the biosimilar and the original product, and that the biosimilar will function in a patient's body in exactly the same way as the reference biologic.

Development process of biosimilars:



The biosimilar development process occurs in three major stages: characterization and perfecting the process, confirmation of bio similarity and approval.

Step – 1 Product development, Characterization and perfecting the process.

- The initial step in development is to have a comprehensive grasp of the reference biology by looking at its structure and function.
- The next step is to build the manufacturing process that produces the very comparable therapy after this information is acquired.
- A biosimilar molecule is methodically engineered to match the medicine's quality and the qualities that were determined during the characterization stage using cutting-edge biological development technology and extremely sensitive analytical instruments.
- Every step of the manufacturing process is optimized by repetition in this iterative process. This approach is repeated until the manufacturing procedure reliably yields a molecular structure that is strikingly comparable to the reference medication.

Step- 2 Biosimilar conformation via studies and regulatory cooperation.

- The next step starts once analysis and testing show that the biosimilar and the reference biologic medication are similar.
- After reviewing all the data, the FDA decides whether any more clinical or non-clinical investigations are necessary to verify biosimilarity and interchangeability.
- For biosimilars to be approved in highly regulated markets like the EU, US, Japan, Canada, and Australia, clinical trials are typically necessary.
- However, the data supplied will determine the parameters and extent of biosimilar clinical studies.
- For example, there is strong and compelling analytical data and more data is needed, a more customized clinical trial approach might offer a more efficient means of proving biosimilarity and interchangeability.

Step – 3 Approval process

- A robust regulatory framework for biosimilars. The EU has a strong legal framework that was established in 2004 and includes a specific pathway for the licensing of biosimilars.
- Since the first biosimilar, the growth hormone somatropin, was approved in 2006, the EU has been at the forefront of the regulation of biosimilars.
- Since then, the European Union has approved the greatest number of biosimilars globally, resulting in the greatest amount of usage and safety data.

- The European Medicines Agency (EMA) has released scientific recommendations over the years to assist developers in meeting the stringent regulatory requirements for biosimilar approval.
- The guidelines have changed throughout time to reflect growing clinical usage experience as well as the quick breakthroughs in biotechnology and analytical sciences.

Process for approval of biosimilars in the EU:

- All biotechnology-produced medications as well as those for particular uses need to be approved by the European Medicines Agency (EMA) using the so-called "centralised procedure."
- Because they are produced using biotechnology, almost all biosimilars that have been approved for use in the EU have done so through central approval processes.
- Certain biosimilars, including certain low-molecular-weight heparins made from pig intestinal mucosa, might receive national approval.
- The EMA's scientific committees on human pharmaceuticals and marketing authorization review data submitted by companies applying for marketing authorization on safety (the CHMP and PRAC), as well as by biosimilar experts (the Biosimilar Working Party) and EU experts on biological medicines (the Biologics Working Party).
- Following EMA evaluation, a scientific opinion is produced and forwarded to the European Commission, which eventually approves a marketing authorization for the entire EU.

Data requirements for approval:

- For any biological medicine with a new active substance, a positive benefit risk balance is determined mainly from evidence of safety and efficacy in pivotal trials in humans.
- A positive benefit risk balance is based on demonstrating biosimilarity, i.e. that the active substance is highly similar to the reference medicine.
- This is achieved via comprehensive comparability studies with the reference medicine

Comparative data requirements:

- "Comparability studies" play a major role in the development of biosimilars by demonstrating their biosimilarity to the reference medication. This entails a thorough side-by-side comparison between the reference drug and the biosimilar.
- Comparability is thought of as a methodical procedure customized for every product based on information from the first quality comparability.
- The goal of studies1 (step 1) is to rule out variations in clinical performance between the reference medicine and the biosimilar. Studies2 (step 3) is used to assess the type and extent of non-clinical (step 2) and clinical studies (step 3) required in the next level of development.
- A well-established scientific tenet of regulatory science is comparability: many comparative quality investigations demonstrate the striking similarities between biological activity and physical attributes.
- Studies comparing clinical and non-clinical aspects that bolster the authorization of a biosimilar eliminate variations that could impact the medication's effectiveness and safety.
- The approval of biosimilars expands on the body of scientific data regarding the efficacy and safety of the reference reduced requirement for clinical data due to the knowledge acquired throughout its clinical use.
- The clinical development program for the reference drug does not require replication in its entirety from a scientific and regulatory perspective. This implies that no needless clinical trials involving patients or healthy volunteers will take place.

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