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Research Article

BIOSIMILARS- BALANCING COST AND EFFICACY

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A B S T R A C T

Biologic medicines have led to significant advances in the treatment of patients suffering from serious illnesses. Biologic medicines are large, complex molecules that are made in living cells grown in a laboratory. They are often 200 to 1,000 times the size of a small molecule drug such as aspirin and are much more difficult to manufacture because of their complex structure. It is impossible for a different manufacturer to make an exact replica of a biologic medicine due to several factors, including the inherent complexity of biologics and the proprietary manufacturing process of the original biologic medicine, often referred to as the reference product. It is because of this that copies of biological products are referred to as "biosimilars"; they are highly SIMILAR but not identical to the biologic upon which they are based. Biosimilars have the potential to offer patients and physicians additional options for the treatment of serious illnesses.1 Large-scale production of highquality, reliably supplied biosimilars requires commitment, highly specialized biologics knowledge and experience, infrastructure and capital investment.

INTRODUCTION

Currently one of the fastest growing segments of the pharmaceutical industry are "Biologics". They refer broadly to substances produced by living cells using biotechnology (i.e recombinant DNA technology, controlled gene expression, or antibody technologies), which have introduced many new treatments to life-threatening and rare illnesses such as cancer, diabetes, anemia, rheumatoid arthritis and multiple sclerosis[1]. Biological Medicine includes wide range of substances like recombinant hormones, growth factors, blood products, monoclonal antibody-based products, recombinant vaccines, and advanced technology products (gene and cell therapy biological products)[2].

'Biosimilars', also known as "similar biologics" are medicines that are similar to another biological medicines which has already been authorised for use. They are considered as generic versions of biologics[3]. This term is referred to as "biosimilars" in Europe, "follow-on pharmaceuticals" in the US and Japan, "subsequent entry biologics" in Canada, "biocomparables" in Mexico and The Indian authorities use the term "similar biologics". Such products are developed after the loss of patent protection by many first generation innovator biological products. The introducion of a biosimilar to an innovator product is far more complex procedure unlike the process of introducing a generic equivalent of an original chemical based drug which is less complicated. This is because-

1. biologics generally exhibit high molecular complexity
2. biologics are produced by cells in culture or whole organisms
3. major changes in the product can occur due to very minor changes in the process.

What is a "Reference Product"?

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and effectiveness data. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful differences[4].

Biosimilar product

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product[4].

What does it mean to be "highly similar"?

A manufacturer developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing (i.e., characterizing) the structure and function of both the reference product and the proposed biosimilar. Stateof-the-art technology is used to compare characteristics of the products, such as purity, chemical identity, and bioactivity[5]. The manufacturer uses results from these comparative tests, along with other information, to demonstrate that the biosimilar is highly

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similar to the reference product. Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. For example, these could include minor differences in the stabilizer or buffer compared to what is used in the reference product. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by FDA to ensure the biosimilar meets FDA's high approval standards[4].

What does it mean to have "no clinically meaningful differences"?

A manufacturer must also demonstrate that its proposed biosimilar product has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness). This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies[5].

What is an interchangeable product?

An interchangeable product is a biosimilar product that meets additional requirements outlined by the Biologics Price Competition and Innovation Act. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient[4]. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated. An interchangeable product may be substituted for the reference product without the involvement of the prescriber. FDA's high standards for approval should assure health care providers that they can be confident in the safety and effectiveness of an interchangeable product, just as they would be for an FDA-approved reference product.

What is the difference between a biosimilar and an interchangeable product?

As mentioned above, an interchangeable product, in addition to being biosimilar, meets additional requirements based on further evaluation and testing of the product. A manufacturer of a proposed interchangeable product will need to provide additional information to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for a product that is administered to a patient more than once, a manufacturer will need to provide data and information to evaluate the risk, in terms of safety and decreased efficacy, of alternating or switching between the products. As a result, a product approved as an interchangeable product means that FDA has concluded it may be substituted for the reference product without consulting the prescriber[6].

For example, say a patient self-administers a biological product by injection to treat their rheumatoid arthritis. To receive the biosimilar instead of the reference product, the patient may need a prescription from a health care prescriber written specifically for that biosimilar. However, once a product is approved by FDA as interchangeable, the patient may be able to take a prescription for the reference product to the pharmacy and, depending on the state, the pharmacist could substitute the interchangeable product for the reference product without consulting the prescriber

Biologics versus small-molecule drugs

Biologics and small-molecule drugs have significant difference because of difference in origin. Chemical methods are generally used to produce small-molecule drugs whereas biological products are synthesized usually by cells or living organisms. The difference in origin leads to difference in structure, composition, manufacturing methods and equipment, intellectual property, formulation, handling, dosing, regulation, and marketing. As comparison to synthetic small molecules, biologics are 100 to 1000 times larger in size, having several hundred amino acids and biochemically joined together in a defined sequence by peptide bonds to form a polypeptide. In contrast, generic drugs are far smaller, i.e molecular weight < 1000, self-contained, organic molecules that are chemically synthesized. The more the size of molecule, the greater is the number of atoms that make up its structure and the greater its complexity. Therefore it is concluded that biologics are more complex than low molecular weight drugs, consisting of primary (amino acid sequence) and secondary (α-helix and β-pleated sheet) structures, which are folded into complicated 3D tertiary structures. In some biopharmaceuticals, stable associations of tertiary structures of individual proteins form a quaternary structure. After synthesis, these structures are often further modified by post-translational modifications such as glycosylation or sialylation, which may be crucial for biological activity[7].

Regulation aspects of biosimilars

A biosimilar product application must include data demonstrating biosimilarity to the reference product. This usually includes data from-

- Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- Animal studies, including an assessment of toxicity
- A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study[4].

In addition to the data listed above, an application for an interchangeable product must also include information or data demonstrating that:

- The proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient
- For a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products.

Need for abbreviated pathway for biologics:

Biological products are the fastest-growing class of therapeutic products in the United States and account for a substantial and increasing portion of health care costs. Congress, through the Biologics Price Competition and Innovation Act, created an

abbreviated approval pathway to provide the public with greater access to safe and effective biological products. This pathway provides more treatment options, potentially lowering health care costs through competition and increasing access to lifesaving medications[5].

Can a biosimilar be approved for an indication that is approved for the reference product even if the biosimilar is not directly studied in that indication?

A biosimilar product may be approved for an indication without direct studies of the biosimilar in that indication. If the total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer. This concept is called "extrapolation" and is critical to the goals of an abbreviated pathway-improving access and options at a potentially lower cost. Extrapolation is based on

1. all available data and information in the biosimilar application,
2. FDA's previous finding of safety and efficacy for other approved indications for the reference product
3. knowledge and consideration of various scientific factors for each indication.

Extrapolation is not an assumption that the data from one directly studied indication or population alone is sufficient to support approval in a different non-studied indication or population. The biosimilar manufacturer must provide scientific justification to support extrapolation. These scientific justification factors include knowledge of the mechanism(s) of action, PK, PD, efficacy, safety, and immunogenicity of the reference product in each of its approved indications. FDA evaluates all of the biosimilar product data to assess whether there are differences between the biosimilar and the reference product that may affect these scientific factors in any of the indications or populations not directly studied by the biosimilar manufacturer. If no such differences are identified, approval of the biosimilar for other non-studied indications or populations is generally supported.

Currently available biosimilars

Table shows list of US-FDA approved biosimilars and their reference products updated on December 2017

Drug Product	Company	Reference Product and Sponsor	Marketing Status	FDA Approval Date
Mvasi™ (bevacizumab-awwb)	Amgen Allergan	Genentech/Roche Avastin® (bevacizumab)	Not available	Approved 9/14/2017
Cyltezo™ (adalimumab-adbm)	Boehringer Ingelheim International GmbH	AbbVie Humira® (adalimumab)	Not available	Approved 8/25/2017
Renflexis® (infliximab-abda)	Samsung Bioepis	Janssen Remicade® (infliximab)	Launched July 2017	Approved 4/21/2017
Amjevita® (adalimumab-atto)	Amgen	AbbVie Humira® (adalimumab)	Not Available	Approved 9/23/2016
Erelzi ® (etanercept-szzs)	Sandoz	Amgen Embrel® (etanercept)	Not Available	Approved 8/30/2016
Inflectra® (infliximab-dyyb)	Celltrion/Pfizer	Janssen Remicade® (infliximab)	Launched Nov. 2016	Approved 4/05/2016
Zarxio® (filgrastim-sndz)	Sandoz	Amgen Neupogen® (filgrastim)	Launched Sept. 2015	Approved 03/06/2015
Ogivri® (trastuzumab-dkst)	Mylan/Biocon	Roche/Genentech Herceptin® (traztuzumab)	Not Available	Approved 12/01/2017
Ixifi® (infliximab-qbtx)	Pfizer	Janssen Remicade® (infliximab)	Not Available	Approved 12/13/2017

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