Current scenario of biosimilar

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Abstract
Biosimilar has gained popularity in past I past few years. A biosimilar is a formally regulated and approved duplicate of an originator biologic therapy. Globally, we are seeing that a growing number of biosimilar applications and approvals. The progress of a biosimilar is significantly more complex and expensive than a small molecule generic product. The medication of many diseases, particularly cancer, has been extremely impacted by the overview of biologic therapies (biologics), which are integrated into the treatment algorithms of most oncology clinical practice guidelines. Emerging market regulators should be authorised to make the risk-benefit decisions that are most suitable for the healthcare system in their country. In the last few years, India has seen a robust development in its biosimilar portfolio. The Indian biosimilar market is composed for big growth, augured by the launch of new products, growing acceptance of biosimilar. This review discusses the current state of knowledge on biosimilar.

Keywords: Biosimilar, popularity, originator biologic therapy

1. Introduction
Biologics
The term biologics originates from the word biology that means “the science of living organisms”. Biologics represent one of the fastest growing segment of the pharmaceutical industry. 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 of life threatening and rare illness such as cancer, diabetes, anaemia, rheumatoid arthritis and multiple sclerosis [1]. Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs [5].

Type of Biologics

Reference Product
A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared [5]. A Reference Biologic is utilized as the comparator for comparability studies with the Similar Biologic in command to show Similarity in terms of safety, efficacy and quality. In India, a reference biologic is one which has been granted a marketing authorization in India by DCGI on the basis of a complete dossier and with a history of safe use in India [3].
Biosimilars
A biosimilar or similar biologics can be defined as a biological product which is formed by genetic engineering techniques and is “similar” in terms of safety, efficacy and quality to a reference biologic [4].

Who Definition
“A bio therapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference bio therapeutic product” [5].

USFDA Definition
A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product [7].

2. Characteristics of Biosimilar
- High molecular complexity
- Quite delicate to changes in manufacturing processes
- Variances in impurities and/or breakdown products can have serious health implications
Copies of biologics might achieve differently than the original exclusive version of the Products [6].

3. Advantages of Biosimilars
- There is huge market needs and growing affordability for Biosimilars in universal and domestic market.
- Development and manufacturing of Biosimilars are improved by existing manufacturing technology [7].
- Due to no investment in phase I-II of clinical trials, Biosimilars are existing at cheaper prices than the reference products, so treatment price with Biosimilars is minor than innovators biological drug [8].

4. Disadvantages of Biosimilars
- Biosimilars are not as much of stable as chemical based pharmaceuticals and thus essential cold chain distribution and have a shorter shelf life. This increases the price and complexity of distribution.
- The cost of development will be importantly higher than for chemical based generics.
- The required capital venture in property plant and equipment and the cost of manufacturing will be much greater for Biosimilars than for generic drugs [7].

5. Regulatory Pathway for approval of Biosimilars
The leading challenges faced by biosimilar drug developers is proving the equipollence or similar attribute of their biological drug to the reference product because of great variation in properties and even miniature alterations can lead to unacceptable deviations in safety and efficacy resulting into the prerequisite of class-concrete guidelines for several intricate molecules of biological [9]. There are different terms used for biosimilar by different regulatory bodies as shown in

<table>
<thead>
<tr>
<th>Regulatory bodies</th>
<th>Terminology used for Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-FDA</td>
<td>Follow on Biologics</td>
</tr>
<tr>
<td>WHO</td>
<td>Similar Bio therapeutic Product</td>
</tr>
<tr>
<td>India</td>
<td>Similar Biologics</td>
</tr>
<tr>
<td>Europe</td>
<td>Biosimilar</td>
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<tr>
<td>Brazil</td>
<td>Follow on Biologics</td>
</tr>
<tr>
<td>Canada</td>
<td>Subsequent Entry Biologics</td>
</tr>
<tr>
<td>Japan</td>
<td>Follow on Biologics</td>
</tr>
</tbody>
</table>

Regulatory Framework in India
Regulatory Guidelines for Biosimilars in India
The regulatory bodies responsible for approval of ‘similar biologics’ in India are the Department of Biotechnology (DBT – under the Ministry of Science and Technology), through its Review Committee on Genetic Manipulation (RCGM), and the CDSCO (under the Ministry of Health and Family Welfare) [10].

Responsible Establishments for the Authorization Process
The competent authorities associated with in the approval process are as follows:
- Review Committee on Genetic Manipulation (RCGM)
- Genetic Engineering Appraisal Committee (GEAC)
- Central Drugs Standard Control Organization (CDSCO)

Appropriate Regulations and guiding principle: Drug and Cosmetics Act 1945 and numerous guidelines for hazardous microorganisms/genetically engineered organisms or cells, 1989 regulate Similar Biologics for the production, utilize, import, export and collected. The list of several guidelines support in development of Similar Biologics are shown in following [11].

Table 1: Various Biosimilar terminologies used by different regulatory bodies.
The Pharma Innovation Journal

- Submission of Clinical Trial Application for evaluation Safety and Efficacy.
- Requirement for permission New Drug Approval.
- Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/ Biologics Products.

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**Guidelines and Handbook for Institutional Biosafety Committee (IBSc)**

**Guidance Documents for Regulatory Approval of Stem Cells and Cell based Products**

**Guidelines for generating Preclinical and Clinical Data for rDNA vaccines Diagnostics and Biologics Products**

**Guidelines on Good Distribution Practice for Biological Products**

**Pharmacovigilance Requirements for Biological Products**

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Fig 1: Various Guidelines for Biosimilars in India

**Regulatory Pathway for Biosimilars in India**

The Timeline taken by Regulatory Authority for approval of Biosimilar is given in the following table:

<table>
<thead>
<tr>
<th>Procure</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCGM approval for pre-clinical animal studies</td>
<td>45 Days</td>
</tr>
<tr>
<td>DCGI approval for Human Clinical Trials protocol</td>
<td>45 Days</td>
</tr>
<tr>
<td>DCGI examination of clinical trial data and response</td>
<td>90 Days</td>
</tr>
<tr>
<td>DCGI &amp; GEAC decisions (simultaneous)</td>
<td>45 Days</td>
</tr>
</tbody>
</table>

**Table 2: Timeline taken by regulatory committee/competent authorities.**

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**Biosimilar approval pathway in India**

- **Product Development**
  - Approval from IBSc
  - Approval from DTB
- **Animal Toxicity Studies**
  - Protocol to be designed as per schedule Y and approved by RCGM and DBT
  - Study conducted as per GLP
- **Clinical Trial**
  - Protocol approval by DCGI and ethics committee
  - Mfg license is needed for clinical trial along with GMP certificate
- **Marketing And Manufacturing Licence**
  - Clinical trial report submitted to DCGI and dossier approved by DCGI
  - MFG license issued after inspection of facility
- **Testing By NIB**
  - First three batches need to be tested by NIB
- **Post Approval Committee**
  - PMS mandatory for atleast 4 years
  - Every 6 months safety reporting to DCGI for 2 years
  - Any process change need to be approved by DCGI

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Fig 2: Approval Pathway of Biosimilars in India

The general regulatory pathway for the approval of the biosimilar in India is shown in figure. The regulatory pathway of biosimilar is bit different from the normal pathway for their approval [12].
### Top Biosimilar Products in India

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Indication/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intacept</td>
<td>Intas</td>
<td>Rheumatoid Arthritis, Psoriatic arthritis</td>
</tr>
<tr>
<td>EPOFER</td>
<td>Emcure</td>
<td>Anaemia</td>
</tr>
<tr>
<td>GRPFEEL</td>
<td>Dr. Reddy’s</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>RituxiRel</td>
<td>Reliance Life Science</td>
<td>Non-Hodgkin’s Lymphoma, Rheumatoid arthritis</td>
</tr>
<tr>
<td>EXEMPTIA</td>
<td>Zydus Cadila</td>
<td>ankylosing spondylitis</td>
</tr>
</tbody>
</table>

### Regulatory Framework in USA

**FDA Approval Pathway**

It is important to note that there are currently two distinct FDA approval pathways in use for biologics. Some have been approved under the Federal Food Drug and Cosmetic Act as ‘drugs’, while others have been approved as ‘biologics’ under the Public Health Service Act. By March 2020, all biologics will be reviewed under the Public Health Service Act. For now, if the originator biologic product was originally approved as a ‘drug’, then a new version of that product (i.e. a product which depends at least in part on the data of the originator) is known as a ‘follow-on biologic’ or ‘follow-on protein’ as opposed to a biosimilar. The diagram below shows the different FDA drug approval pathways.

- **‘Follow-on biologics’** approved via the 505(b) (2) pathway between 1998 and 2006 comprise versions of recombinant glucagon, hyaluronidase, calcitonin salmon and somatropin. The newest product to be approved via the 505(b) (2) pathway (in January 2016) was a follow-on version of insulin glargine [13].

### 6. Biologics products

These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including therapeutic proteins (such as filgrastim), monoclonal antibodies (such as adalimumab), and vaccines (such as those for influenza and tetanus).

**Reference Products**

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.

**Biosimilars Products**

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. These two standards are described further below.

To achieve a biosimilar designation from the FDA, the protein must have no clinically meaningful differences in terms of safety and effectiveness from the original protein, known as the reference product.
Interchangeable Products
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 [14].

**Top Selling Products in USA in 2017**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Indication/Disease</th>
<th>Sales in 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira</td>
<td>AbbVie</td>
<td>Rheumatoid arthritis, Plaque psoriasis, Crohn’s Disease,</td>
<td>$18.4 b</td>
</tr>
<tr>
<td>Rituxan</td>
<td>Roche</td>
<td>Non-Hodgkin’s Lymphoma,</td>
<td>$9.2 b</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Pfizer/Amgen</td>
<td>Rheumatoid arthritis</td>
<td>$7.9 b</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Roche</td>
<td>HER2+Breast Cancer</td>
<td>$7.4 b</td>
</tr>
<tr>
<td>Remicade</td>
<td>Johnson &amp; Johnson/ Merck &amp; Co</td>
<td>Rheumatoid arthritis, Ulcerative Colitis</td>
<td>$7.1 b</td>
</tr>
</tbody>
</table>

7. Worldwide Scenario of Biosimilars
The worldwide biosimilar advertise is driven basically by the blockbuster items and the related research pipeline. Presently, there is just a predetermined number of biosimilar in the market, confined to the classes of development hormones, development factors, monoclonal antibodies, combination proteins, interferons, and low-atomic weight heparins (LMWHs). Though the residential markets are more thrived in the present circumstance, coordinated efforts and organizations demonstrating as prominent systems to pick up piece of the overall industry universally. The 60+ biosimilar in the development pipeline include medications in therapeutic areas such As oncology, immunology, and diabetes, with biosimilar producers showing particular interest in leading Biologics with recent or pending patent expiry, including Avastin, Humira, and Levenir.

As biosimilars are broadly utilized as a part of counteractive action and treatment of a scope of interminable ailments, for example, diabetes, tumors, CVDs, immune system illnesses, rheumatoid joint pain, kidney disappointment, development hormone inadequacy, haematological maladies, and irresistible infections, the interest for biosimilar is probably going to assemble force inside the following couple of years [16].

Marked down biosimilar costs will keep on holding a noteworthy effect on the general biosimilar deals, as patients will remain the key recipients. Trailblazer's cost dropping with substantial rebates is an ongoing, continuous pattern among the makers situated in advancing biosimilar markets. In the recent past, several blockbuster biologic drugs of major pharmaceuticals companies, such as Remicade, Rituxan, Herceptin, Enbrel, Lantus, and others expired. In the coming decade, there would be a rise in the patent expiration of several existing biological drugs, such as Erbitux, Avastin, Ocrenica, and others, which would provide an opportunity for many innovator companies as well as generic manufacturers to offer services, specially tailored toward biosimilars. In addition, factors, such as cost effectiveness nature of biosimilars, rising acceptance and adoption by various stakeholders with the need of diversification in technology and business models, are expected to drive the global biosimilar market.

The global biosimilar market has been segmented by product class and geography. By geography, it has been segmented into North America, Europe, Asia-Pacific, Middle East & Africa, and South America. North America accounted for the largest share, accounting for around 30% of the global market, in 2017 [17].

**Biosimilar market in India**
India shares 75% of biosimilar market, in which 30 biosimilar products are marketed out of 40 biological products. First biosimilar was registered and marketed in India for a hepatitis B in 2000. As of late more than 50 biopharmaceutical items have been affirmed in India, with the greater part of them being biosimilar [20].

**Conclusion**
Biosimilar will expected become an progressively important part of the pharmaceutical Ecosystem. Though, they continue to face barriers to adoption, including questions of interchangeability, a typical lack of approval for all the reference biologic’s indications, the need for biosimilar manufacturers to negotiate with payers, the challenge of overcoming unique patent dynamics, and innovators’ established positions within the physician community. Biosimilar maker needs to face unusual problems in the development, clinical improvement, manufacturing, registration and product marketing contrasted with customary generics. India's characteristic quality in pharmaceutical marketing has been the back to end up one of the key player being developed and maker of biosimilar [19].
References