Biosimilars: Its Present and Future

The biosimilars industry has been growing stupendously. The Indian biogenerics industry is poised to exploit the opportunity they did in the case of generics. This article aims to identify and analyse the biosimilars market and the regulatory scenario in India.

Shreya Dave
Associate
K&S Partners

Saurabh Anand
Associate
K&S Partners

Indian Pharmaceutical Industry is a highly potential lucrative investment target owing to allowance of 100 per cent Foreign Direct Investment (FDI). Collaboration or alliance between multi-national pharmaceutical companies and Indian companies has resulted in newer, qualitative and cost effective products using advanced technology. As opposed to greenfield investments, brownfield investments in the Indian pharma industry, require prior approval of the Foreign Investment Promotion Board (FIPB), Department of Economic Affairs and Ministry of Finance. This, however, does not discourage any foreign investment as given the regulatory and procedural protocols mandated in India, greenfield investments are a more preferred option. It should be further noted that 100 per cent FDI is allowed in pharmaceuticals provided the venture is neither involved in use of recombinant technology nor does it attract compulsory license.[1] Essentially, FDI policy acts as to create a balance between requirements of India's huge population on one hand and capital requirements of the sector on the other.

National Pharmaceutical Pricing Policy (NPPP), was formulated to monitor essentiality of drugs, control of formulation prices and market based pricing, thereby ensuring that there is no price surge in the pharmaceutical industry. Further, post Drug Price Control Order (DPCO) of 2013, Indian pharmaceutical market witnessed a compound annual growth rate of 12 per cent.[2] It is estimated that Indian Pharma Industry is fourth in volume and thirteenth in value globally.[3]

Similar Biologics

After generics, Indian pharma industry has received a major boost owing to emergence of similar biologics whose growth has only increased in the last two decades. Before delving further into the nuances of drug approvals and patents surrounding similar biologics, we understand what are similar biologics or biosimilars as under.

When the patent for the original molecule expires, other companies can launch follow- on versions of the same. If the molecule is chemically synthesized, the follow-on molecule is called a "generic" whereas when the molecule is a biological (like a monoclonal antibody), the follow-on molecule is called a biosimilar. "Generics" and "Biosimilars" are developed by comparing their properties to the original molecule, which is called a reference product. Any follow-on biological product that is approved based on evaluation of comparative data to the reference product is called a biosimilar. These biosimilars are similar to the original or reference drugs in terms of safety, efficacy and quality and are alternatively termed as similar biologics. A similar biologic can only be developed against a licensed reference biologic that

Biologic (Brand name)	INN Name	US Expiration	EP Expiration
Avastin	Bevacizumab	2019	2022
Herceptin	Trastuzumab	2019	2014
Humira	Adalimumab	2016	2018
Synagis	Palivizumab	2015	2015

Table 1

has been approved using a complete data package in India.[4] The demonstration of bioequivalence of the generic medicine with a reference product is usually appropriate and sufficient to infer therapeutic equivalence between the generic medicine and the reference product.[5]

It is undisputed fact that biological drugs are synthesised by cells of living organisms, as opposed to chemical drugs which are produced by chemical synthesis. Owing to the complexity in the molecular arrangement and manufacturing process of a biological drug, it is not possible to replicate the structure and steps involved in the manufacture of the innovator biological drug and to produce an identical follow-on biological drug. Biosimilars, therefore, cannot be generic equivalents of the innovator biological drug. The generic drugs are characterised by their chemical and therapeutic equivalence to the original, low molecular weight chemical drugs. the similarity with the referenced biologic has to be establish not merely in the manner of bioequivalence regime but also on other facets and requirement under bio-similar as well. Thus, in case of similar biologics, similarity has to be seen and examined on various facets including structural and physicochemical properties, biological activities, purities and impurities etc. Thus, biosimilars cannot be generic equivalents of the innovator biological drug.

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It is estimated that by 2020, as illustrated in the Table 1[6] (See previous page), patents on several biological products with global sales of more than USD 67 billion will expire.

The global biosimilar market is highly skewed with Sandoz (a part of Novartis group), Teva Pharmaceutical Industries Ltd. and Hospira (completely acquired by Pfizer) occupying a bulky share of the market. Further, Indian pharmaceutical companies like Dr Reddy's Laboratories, Biocon Ltd., Intas Biopharmaceuticals Ltd. etc. are amongst a few major players in the global market too. Further, the period of 2010-2015 has witnessed a series of strategic alliances and acquisitions of Indian pharmaceutical companies by pharmaceutical MNCs in this regard.

Similar Biologics in India: Governing Regulations

Indian "Guidelines on Similar Biologics"[7] released in June 2012 by Department of Biotechnology (DBT) and its Central Drugs Standard Control Organization (CDSCO), define 'similar biologic' as biological product/drug produced by genetic engineering techniques and claimed to be 'similar' in terms of safety, efficacy and quality to a reference biologic, 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. The guidelines further clarify that only a product that was licensed on the basis of a full registration dossier can serve as reference biologic. As mentioned before, a reference biologic is used as the comparator for head-to-head comparability studies with the similar biologic in order to show similarity in terms of safety, efficacy and quality.

The similar biologics are regulated as per the Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended from time to time) and Rules for the manufacture, use, import, export and storage of hazardous microorganisms/ genetically engineered organisms or cells, 1989 (Rules, 1989) notified under the Environment (Protection) Act, 1986. Additionally, amongst other regulatory mechanisms, CDSCO Guidance for Industry (2008) and Recombinant DNA Safety guidelines, 1990 are also applicable on similar biologics.

Competent statutory authorities involved in the approval process of similar biologics are broadly as under:

- **Review Committee on Genetic Manipulation (RCGM)**
  - authorizing import/export for research and development and review of data up to preclinical evaluation.

- **Genetic Engineering Advising Committee (GEAC)**[8]
  - approval of activities involving large scale use of genetically engineered organisms and products thereof in research and development, industrial production, environmental release and field applications.

- **Central Drugs Standard Control Organization (CDSCO)**
  - for grant of import/export license, clinical trial approval and permission for marketing and manufacturing.

Central Drugs Standard Control Organization (CDSCO) and Department of Biology (DBT) on March 26th of 2016 had proposed draft Guidelines on Similar Biologics, 2016 for suggestions and comments the Biosimilar products and for their manufacturers. Although the revised guidelines have not been finalised, few observations regarding the same have been elucidated as under:

"A reference biologic is used as the comparator for head-to-head comparability studies with the similar biologic in order to show similarity in terms of safety, efficacy and quality."

- As per the draft guidelines, if reference biologic (for which the biosimilar is being developed) is not marketed in India, the reference biologic should be licensed in any ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) country.
- To reduce residual risk of similar biologic, additional safety data may be required post market approval in a prescribed manner.
- It is not mandatory to carry out additional non-comparative immunogenicity studies in post marketing if the same has been evaluated in clinical studies.
- With respect to manufacturing, the section on "Fermentation Process Development," has been renamed to "Upstream Process Development."
- Manufacturers are required to provide details of upstream process kinetics data from consistency batches indicating cell growth, product formation, pH, temperature, dissolved oxygen, major nutrient consumption pattern and agitation rate

Roche v Biocon[9]

On 25th April, 2016, Delhi High Court passed India's first judgment in a biosimilar related legal battle. Major issues in the current matter revolved around regulatory protocols, and possible abbreviation of clinical trials for Biosimilars.

In February 2014, Roche sued Biocon and Mylan on account of imminent threat of the introduction of purported biosimilar version of biological drug Trastuzumab, under the brand names CANMAb and HERTRAZ. The major contention of Roche was that the defendants' drugs are, inter alia, being misrepresented as "Trastuzumab", "biosimilar Trastuzumab" and a biosimilar version of HERCEPTIN without following due process In accordance with the Guidelines on Similar Biologics for the purpose of obtaining appropriate approvals.

Major Contention of Roche

a) Defendants have stated in their press statements that they have jointly developed a drug which they claimed is biosimilar to Trastuzumab and that CANMAb and HERTRAZ will become available in India in the first week of February 2014.

b) The undue haste with which the approval was granted (within 3 days of request) by the DCGI suggests that all factors relevant to the approval of a biosimilar drug under the Guidelines on Similar Biologics and under other internationally recognized standards were not taken into consideration at the time of granting such approval.

The Delhi High Court in a detailed judgment, has covered the aspect of Biosimilars, major observations are as follows: -

i. The existing rules framed under the Drugs and Cosmetics Act do not provide the exhaustive mechanism for dealing with the Bio Similar products as there are certain additional aspects which the guidelines insist to be taken into consideration in the process of the grant of the approval in the cases involving similar biologics. Thus, the guidelines are supplemental to the rules framed under the Act and thus it is binding on the office of the DCGI when the CDSCO is headed by DCGI. The guidelines of 2012 thus qualify the test that the same are supplemental to the rules and are not aimed to replace or supplant the existing rules;

ii. Biosimilar drugs are 'new drugs' under Explanation (i) of Rule 122E of the Drugs Rules, and therefore, the entire pre-clinical and clinical data is required to be submitted for their approval. Under Rule 122B(1) (b) and 122B(2) of the Drugs Rules, the application for such approval has to be made to DCGI in Form 44 of the Drugs Rules along with the data in Appendix I. The issue in hand does not pertain to bioequivalence but is in relation to bio-similarity of the drug of innovator.

iii. Biocon's drug is biosimilar and is not identical drug to the innovator drug, it has to be called as "new drug" discovered by Biocon who itself submitted that it has conducted various clinical trials independently. Furthermore, as Biocon's drug is a new drug manufactured in India for the first time by Biocon, thus as per paragraph 1(1)(iv)(a) of Schedule Y all phases of the clinical trials must be conducted in India, and there DCGI had no legal basis for exempting Biocon from conducting Phase I and Phase II of the clinical trials in the present case without assigning any valid reasons

iv. Requirements of conducting Phase I and Phase II clinical trials can be abbreviated as per the settled position throughout, if the regulatory authorities are satisfied that such waiver is
   a) pwemiaaivlw in accordance with the rigorous standards of interchangeability and similarity with the innovator drug under applicable laws;

b) scientifically justified pursuant to complete characterization and pre-clinical studies having been concluded to establish comparability of the follow-on biologic drug with the innovator drug in terms of quality, safety and efficacy.

Only after the fulfilment of these conditions by the follow-on drug manufacturer that the extent of possible reduction of pre-clinical and clinical trial data is determined by the regulatory authority, strictly on a case-by-case basis but never automatically.

In a case of similar nature[10], Roche sued DCGI and Hetero Drugs before the High Court of Delhi to block approvals for biosimilar of Bevacizumab, which is marketed under the name Avastin and is used to treat debilitating ailments like colorectal cancer, non-small cell lung cancer, kidney cancer and ovarian cancer. Roche has filed the aforesaid suit challenging the process followed by a health ministry Subject Expert Committee (SEC) to recommend the copy for use in metatastic colorectal cancer. The present suit is pending adjudication.

Take Aways...

Indian Pharmaceutical industry has been growing by leaps and bounds both in volume and value. Position of law pertaining to generics has been settled by lot of legal precedents over the period of time. In light of the landmark Roche v Biocon[11] judgment, which is one of a kind till date, position of law and the way forward for biosimilar drug manufacturers can be laid down as under:

- **Package Insert**
  If all the clinical trials have been conducted and protocol are complied with by a party strictly as per Act and Rules of local laws and as per Guidelines, the data package insert may be similar as possible with the original innovator. But it shall not be reproduction from the package approval of innovators and there should not be any incorrect and misleading statement by a party.

- **Data exclusivity**
  Unless Government of India frames policy to declare as to whether after expiry of patent, the data in public domain can be used as pathways or not, the regulatory authority can neither disclose nor rely upon the first applicant's data at the time of granting marketing approval to the subsequent applicants. It is for the Government to decide that such protection for certain fixed period to the innovator should be granted or not.

- **Strict Compliance of the Rules**
  If an entity is willing to manufacture "Biosimilars" then it has to apply to DCGI under the appropriate form and the authorities and committees shall decide the said approval application in accordance with the Rules and Guidelines of 2012.

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