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Review Article

REGULATION FOR DEVELOPMENT OF BIOSIMILAR : A REVIEW

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ABSTRACT

Present article signifies the exigency for regulation and regulatory bodies involved in development of biosimilars. The principle for development of biosimilars included opting adequate reference product, manufacturing process optimisation, quality control procedure, preclinical and clinical studies. India's first guidelines were enforced in 2012, with amendments in 2016. Thus, we elaborated the amended guidelines for development of biosimilars.
Keywords: Biosimilars; Manufacturing; Stability; Efficacy; India Guidelines.

INTRODUCTION

Biologicals are pharmaceutical products prepared by recombinant technology via living cells (animal, bacteria, and yeast) to produce three dimensional protein structures, very high molecular weight. Sometimes, they are also classified as speciality drugs. Biosimilars are copied version of biopharmaceutical drugs with similar quality, safety and efficacy. These are approved after or near-by patent expiration of the original biologic products[1-4]. A biosimilar is a copy of a biopharmaceutical/ biologic product, which is similar, however, not identical to the products derived from recombinant DNA technology. These are approved after or near-by patent expiration of the original biologic products.

Various biosimilars available in India are Adalimumab, Rituxumab, Darbepoetin alfa, Infliximab, Follitropin alfa, Abciximab, Trastuzumab, Teriparatide, Pegfilgrastim, Erythropoietin and Human Insulin[5,6]. In 2015, various pharmaceutical companies such as Dr. Reddy's Laboratories and Biocon Limited have spread the biosimilars market in India[7,8]. The international key players in the biosimilars market are Sandoz International GmbH, Hospira Inc., and Teva Pharmaceutical Industries Ltd., Mylan Inc., Amgen, Celltrion Inc., Roche Diagnostics, and Merck KGaA[8]. Even minor changes in the manufacturing process can alter the biosimilars affecting its comparable efficacy, safety and quality to the reference biological. Therefore, highly consistent and robust regulations are required to control its physicochemical properties, evaluate biosimilars in terms of safety, purity and potency. Ultimately, approving and making them available for public use.

HISTORICAL PRESPECTIVE

The first generation of biological products manufactured utilising recombinant technologies was established in the 1980s, and they are now either expired or near-by patent expiration[9]. This has lead to production of their non-innovator, called 'biosimilars' in the European Union. In the United States, biosimilars are known as 'follow-on protein products'. Europe has been following a legal and regulatory pathways for approving biosimilars to be in the market since 2005[10-13], while the United States approved only an overarching guidelines for scientific and quality considerations[14,15].

The first-generation biopharmaceuticals are duplicate of endogenous human proteins, such as erythropoietin, insulin, growth hormones and cytokines. These were developed utilising recombinant DNA (rDNA) technology or hybridoma techniques.3 Recombinant technology has furnished a means of manufacturing a variety of therapeutic proteins. Thus, biopharmaceuticals to become major therapeutic options for a variety of indications[3]. These substances have improved treatment of many diseases, including cancer, anaemia related chronic kidney failure and diabetes. The biopharmaceuticals such as granulocyte colony stimulating factors, erythropoietin, interferons and human growth hormone patent expiry has paced the study and development of biosimilar.

As a result of patent expiration, research-based and pharmaceutical companies are focussing on the opportunity to develop "generic" substitutes for original biologics, referred to as biosimilars. Biosimilars are "similar but not the same" or biosimilars are basically the twin. These are not the clone" to the innovator product[9]. Over 50 biopharmaceutical products have marketing authorisation in India in recent years. About 50% of these biopharmaceuticals were biosimilars. Its biosimilars regulatory pathway was enforced in 2012, however, a proposed guideline is also released by the Central Drugs Standard Control Organization (CDSCO) in 2016. India had already approved more than 25 products "similar biologics". In India, there is need to offer and initiate adequate protections for patentable drugs, particularly biologics that inherently involve huge investments in their research and development, manufacture and clinical development as there is no market exclusivity period[16].

ECONOMICAL STATUS IN INDIA

In India, development of biosimilars cost around 10-20 million USD due to regulatory procedures for their approval. Phase I/II are not conducted for their development, hence, it reduces the cost of biosimilar by 25-40% than the reference product. Compound Annual Growth Rate (CAGR) of +30% is observed in India. Sales are increased from 200 million USD to 580 million USD between 2008-2012[17].

The global biosimilars market is expected to rise from $2.29 Billion in 2015 to $6.22 Billion by 2020, growing at a CAGR of 22.1% [8]. The growth of the global biosimilars market is driven by factors such as growing pressure to diminish healthcare expenditure, growing demand for biosimilar drugs due to their cost effectiveness, augmenting incidences of various diseases, augmenting number of off patented drugs, positive outcome in the ongoing clinical trials, and rising exaction for biosimilars in different therapeutic applications such as rheumatoid arthritis and blood disorders. However, factors such as eminent manufacturing complexities and costs, stringent regulatory requirements in developed and developing countries, and innovative strategies by biologic drug manufacturers to hinder the entry of new players are restraining the growth of this market[8]. Europe is the largest market for biosimilars, followed by Asia Pacific. China and India are objected to grow at the fastest rate[8].

CHALLENGES IN DEVELOPMENT

Biosimilar are different from the generic drugs in terms of size and complexity of the active substances. They have an internal structure heterogeneity that in combination to complex manufacturing process may affect safety and efficacy[3]. These are produced in living cells, thus, makes the final product very sensitive to major and minor changes in production conditions. Immunogenicity is another challenge faced in the development of the biosimilars. These proteins are formulated to imitate human proteins. However, multiple doses are administered for protracted time may lead to an immune response[18]. Moreover, protein molecules could be degraded during processing steps and impurities created in these steps may produce immune reaction. Degradation can occur by one of three mechanisms: glycosylation, contamination and changes to 3D structure.

DEVELOPMENT OF BIOSIMILARS

The development of biosimilars is a vast and complex process. These require a high research for development of biosimilars. The biologic whose patent is near expiry is the mostly opted by various pharmaceutical companies. The company has to develop a consistent and robust manufacturing process so that it can produce batch-wise products with equal physiochemical and biological characteristics. The product is compared to the reference product via preclinical and clinical trials. The similar efficacy, quality and safety of the biosimilars to the reference product is the required output.

NEED FOR REGULATIONS

Guaranteeing consistency in the production of these agents is a difficult task. Augmented befall of pure red cell aplasia (PRCA) in 1998 demonstrated that even one small change in the manufacturing process can alter the product's characteristics[19]. Such intricacy demonstrates that requirements for marketing authorization for these biosimilar products cannot be the same as for low molecular weight generic drugs[2]. Assays for analysis of physicochemical properties and biological properties of biosimilars are necessary to test the resemblance and comparability of a biosimilar against the innovator drug[20]. Physicochemical properties are molecular weight, density and stability. Biological Properties are receptor related activity and immunogenicity. Careful recognition of limitation of available assays is necessary to ensure continued safety and efficacy in the target populations. Analytical assays qualities play a central role in the judgement making for marketing authorization of biosimilar products. There are various detrimental in using biosimilars. Cost of development of high molecular weight biosimilar is higher than low molecular weight generic drug. To maintain their stability, specific handling procedures must be followed. Immunogenicity is also affected by process related impurities. Even with these circumstances, biosimilars have gained an immense market growth globally over a decade.

REGULATORY CONSTRAINTS FOR MARKETING AUTHORISATION OF BIOSIMILARS IN INDIA

The Indian guidelines define a "similar biologic" as a "biological product/drug generated by genetic engineering techniques and claimed to be 'similar' in terms of safety, efficacy and quality to a reference biologic, which has been offered marketing authorization in India by DCGI on the basis of a complete dossier, and with a history of safe use in India." [21] CDSCO and the Department of Biotechnology (DBT) formulated the "Guidelines on Similar Biologics". These guideline emphasize on the regulatory pathway for marketing authorisation of biosimilar in India. It covers the manufacturing aspects and comparing quality, pre-clinical and clinical studies and post market regulatory requirement for them. Though these guidelines are prepared by the CDSCO and DBT, yet, the approval process of a proposed biosimilar include following authorities. These authorities are depicted in Figure 1.

Apart from Guidelines on similar biologics - regulatory requirements for marketing authorization in India, various other regulations and guidelines are applicable for the approval process. Other Indian guidelines and regulations are depicted in Figure 2.

These guidelines focus on the marketing authorisation of product manufactured in India as well as imported for marketing in India. It deals with principle for the development of similar biologics. Development comprises physicochemical and biological characterisation of the product along with comparability exercises confirming quality, safety and efficacy of proposed biosimilar to the reference product. These key specifications for characterisation are mentioned in the Figure 3.

Various products are approved according to these guidelines. A biosimilar by Torrent Pharmaceuticals of Adalimumab was approved in 2016 for Ankylosing spondylitis, Ulcerative colitis, Plaque psoriasis, Psoriatic arthritis and Rheumatoid arthritis. A biosimilar of Rituxumab (Hetero group) sanctioned in 2015 for Lymphoma and Non-Hodgkin's Lymphoma. A biosimilar of Trastuzumab (Biocon) in 2013 for Breast Cancer.

Extrapolation of Efficacy and Safety Data to Other Indications

When biopharmaceutical (prescribed for more than one indication) is used as the reference product for the development of biosimilar. The extrapolation of the safety and efficacy data of the peculiar clinical manifestation (for which clinical studies has been done) of a Similar Biologic to other clinical manifestation may be possible. It is possible

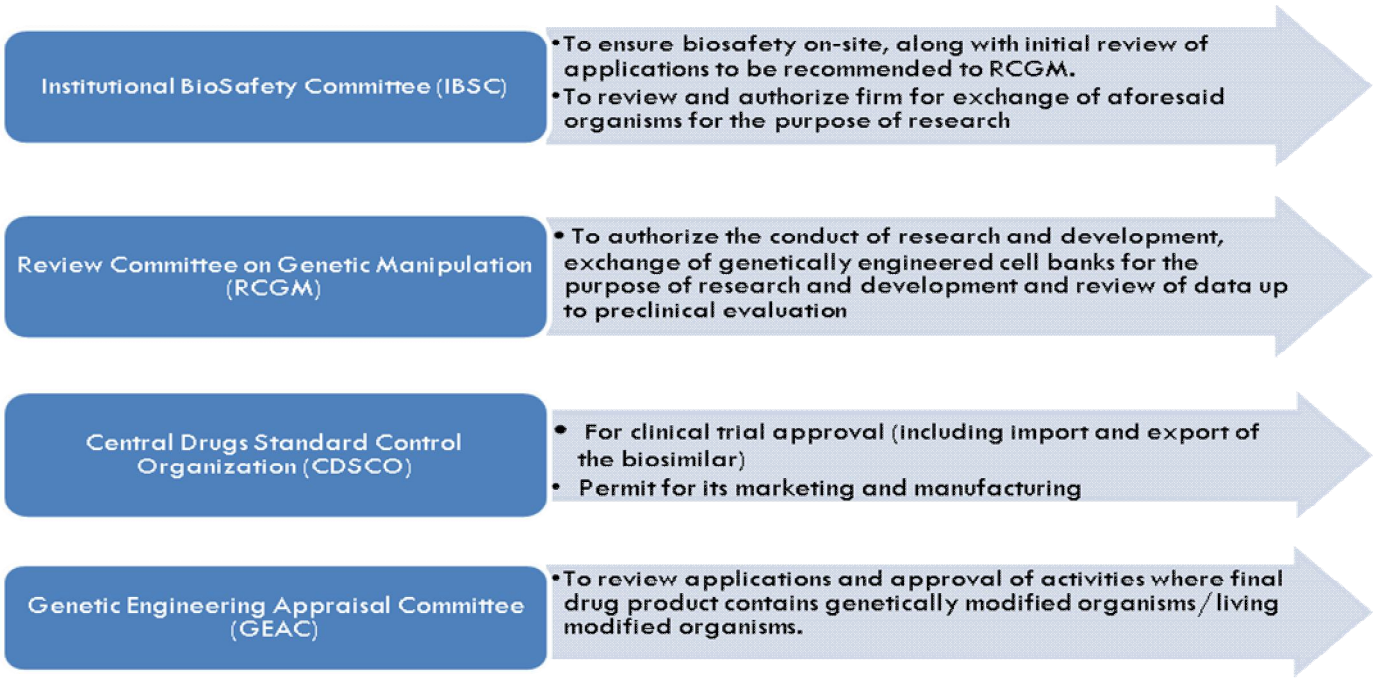


Figure 1: Authorities involved in approval process of biosimilars with their functions

Adapted from: Guidelines on similar biologics-regulatory requirements for marketing authorization in India

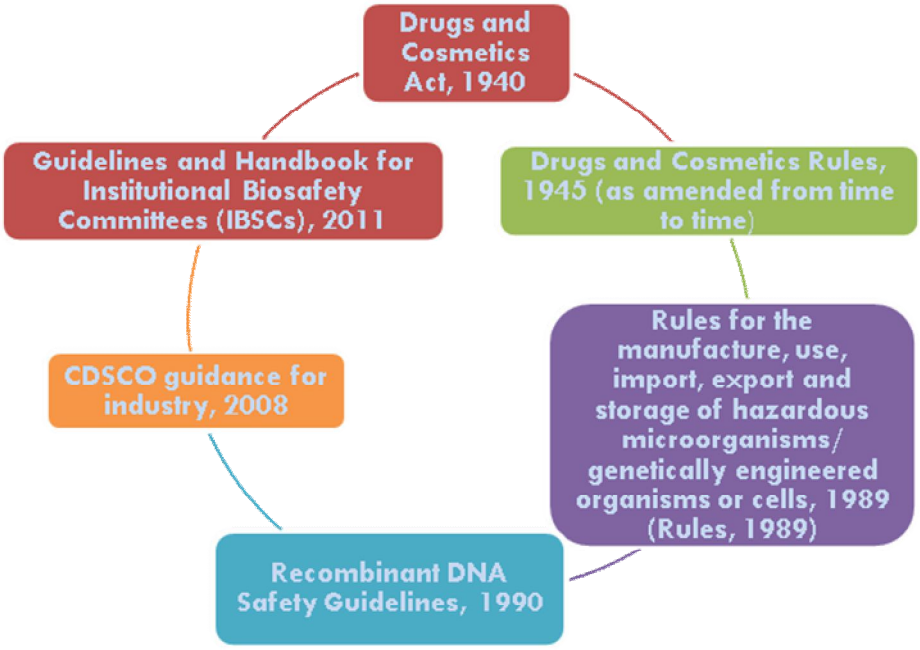
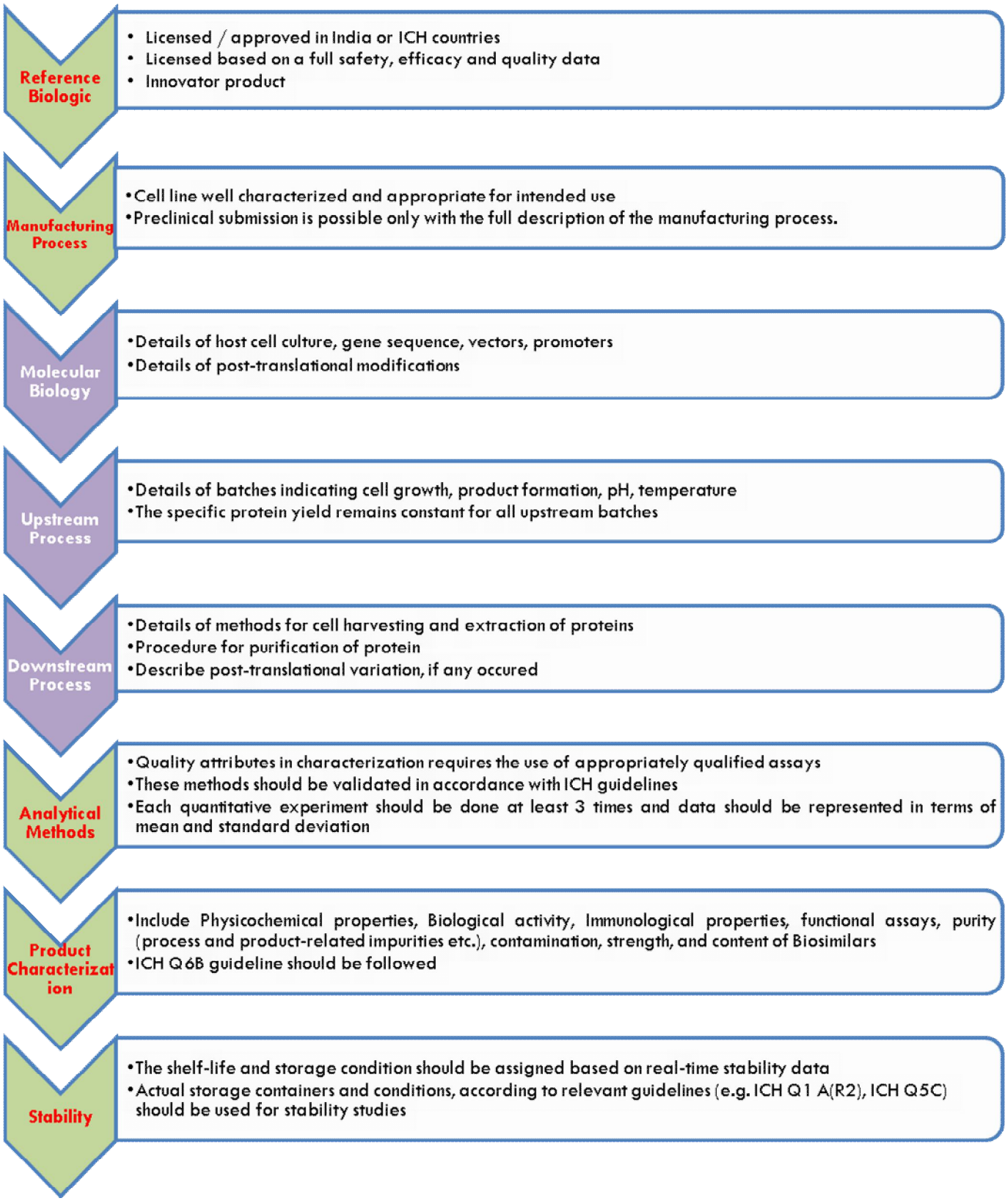


Figure 2: Additional Indian guidelines followed for approval.

Adapted from: Guidelines on similar biologics-regulatory requirements for marketing authorization in India



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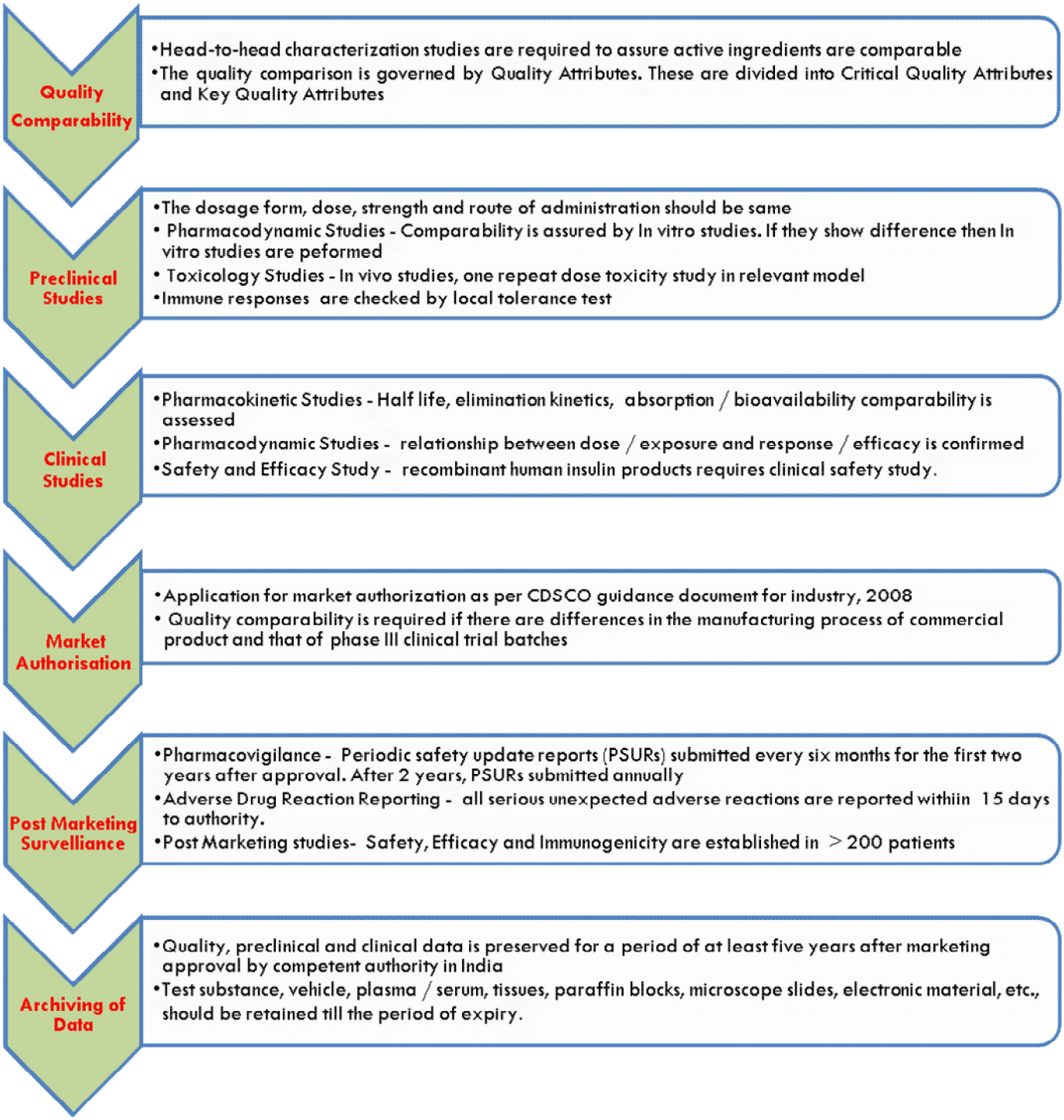

Figure 3: Principles for development of biosimilars

Adapted from: Guidelines on similar biologics-regulatory requirements for marketing authorization in India

under certain circumstances. When it is established that biosimilar is similar to reference biologic in terms of quality, preclinical assessment. The biosimilar has been proved similar in clinical safety and efficacy for one indication (for which clinical studies has been done). Mechanism of action should be identical for various other clinical indications of similar biologics. Same receptor(s) are linked with other clinical indications. However, new indications not mentioned by innovator will need be covered by a separate application.

CONCLUSION

Guidelines are obligatory for comparison of provisions determining the reference product, non – clinical testing strategies, clinical testing strategies, clinical safety, pharmacovigilance requirements and immunogenicity assessments. Development of biosimilar is a sequential process and thus, a firm and congruous regulations are needed for their ratification. Authority must ensure that these regulations are strictly followed so that time and cost involved in development of biosimilars could be minimised.

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