REGULATORY REQUIREMENTS OF 'SIMILAR BIOLOGICS' FOR MARKETING AUTHORIZATION IN INDIA

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REVIEW ARTICLE

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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 optimization, 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; CDSCO, IBSC, Manufacturing; Stability; Efficacy; India Guidelines.

INTRODUCTION

The "Guidelines on Similar Biologic" prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) lay down the regulatory pathway for a Similar Biologic claiming to be Similar to an already authorized Reference Biologic. (1, 2)

A Similar Biologic product is that which is Similar in terms of quality, safety and efficacy to an approved Reference Biological product based on comparability. The guidelines address the regulatory pathway regarding manufacturing process and safety, efficacy and quality aspects for Similar Biologics.

These guidelines also address the pre-market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for Similar Biologics.

These guidelines are for the guidance of all stakeholders and are not meant to substitute or rephrase the Rules made under Drugs & Cosmetics Act, 1940 or any other relevant Acts and are subject to being in conformity with the Drugs & Cosmetics Act and Rules as may be amended from time to time. (3)

Background

CDSCO is the national regulatory authority in India that evaluates safety, efficacy and quality of drugs in the country. DBT through Review Committee on Genetic Manipulation (RCGM) is responsible for overseeing the development and preclinical evaluation of recombinant Biologics. (4)

Presently, several organizations are actively engaged in manufacturing and marketing Similar Biologics in India. So far, these Similar Biologics were approved by RCGM and CDSCO using an abbreviated version of the pathway applicable to new drugs on a case by case basis. Since there are several such products under development in India, both regulatory agencies considered the need to publish a clear regulatory pathway outlining the requirements to ensure comparable safety, efficacy and quality of a Similar Biologic to an authorized reference Biologic.

Objective

Based on demonstration of similarity in the comparative assessment, a Similar Biologic may require reduced preclinical and clinical data package as part of submission for market authorization. (5)

The objective of this document is to provide guidelines to applicants to enable them to understand and comply with the regulatory requirements for the authorization of Similar Biologics in India.

Regulations and Approval for Bio-similar products (1,2,6,7)

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 Central Drugs Standard Control Organization (CDSCO – under the Ministry of Health and Family Welfare).

India announced the release of draft regulatory guidelines for 'similar biologics' at the BIO industry conference in Boston, USA, on 19 June 2012. Finalized guidelines were implemented on 15 September 2012. The guidelines outline a simple abridged procedure for evaluation of 'similar biologics' which have been approved and marketed in India, Europe or USA for more than four years.

India has, by far, demonstrated the greatest acceptance of 'similar biologics'. The first 'similar biologic' was approved and marketed in India for a hepatitis B vaccine in 2000. In recent years over 50 biopharmaceutical products have been approved for marketing in India, with more than half of them being 'similar biologics.

Guidelines

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. Various applicable guidelines are as follows (3,8):

• Recombinant DNA Safety Guidelines, 1990

• Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other biologicals, 1999

• CDSCO guidance for industry, 2008:

i. Submission of Clinical Trial Application for Evaluating Safety and Efficacy

ii. Requirements for permission of New Drugs Approval

iii. Post approval changes in biological products: Quality, Safety and Efficacy Documents

iv. Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products

• Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.

Competent Authorities (9)

The competent authorities involved in the approval process are as follows:

I. Institutional Bio-Safety Committee (IBSC)

IBSC is required to be constituted by any person including research institutions handling hazardous microorganisms and/ or genetically engineered organisms. IBSC is responsible for ensuring biosafety on-site, along with initial review of applications to be recommended to RCGM. IBSC is also assigned with the responsibility to review and authorize firm for exchange of aforesaid organisms for the purpose of research.

II. Review Committee on Genetic Manipulation (RCGM)

RCGM is functioning from the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India. In the context of Similar Biologics, RCGM is responsible for authorizing the conduct of research and development, exchange of genetically engineered cell banks for the purpose of research and development and review of data up to preclinical evaluation.

III. Central Drugs Standard Control Organization (CDSCO)

CDSCO, headed by the Drug Controller General of India (DCGI) is the apex regulatory body under Ministry of Health & Family Welfare (MoHFW), Government of India which is responsible for the approval of clinical trials as well as new drugs. In the context of Similar Biologics, CDSCO is responsible for clinical trial approval (also grants permission for import of drugs for clinical trial and export of clinical samples for biochemical and immunological analysis) and permission for marketing and manufacturing.

Zonal CDSCO is responsible for authorizing import of drugs for examination, test and analysis for research and development**.**

Principles for development of Bio-similar products (10)

Similar Biologic is developed through a sequential process to demonstrate the Similarity by extensive characterization studies revealing the molecular and quality attributes with regard to the Reference Biologic.

Although the extent of testing of the Similar Biologic is likely to be less than that required for the Reference Biologic, it is essential that the testing of the Similar Biologic be sufficient to ensure that the product meets acceptable levels of safety, efficacy and quality to ensure public health in accordance with international guidelines. (WHO 2013).

Generally, a reduction in data requirements is possible for preclinical and /or clinical components of the development program by demonstration of comparability of product (Similarity to authorized Reference Biologic) and the consistency in production process, which may vary depending on the characteristics of the already authorized Reference Biologic.

Principles are followed regarding as (10, 11):

7.1 Selection of reference biologic

7.2 Manufacturing process

7.2.1 Molecular Biology consideration

7.2.2 Up-stream process development

7.2.3 Down-stream process development

7.3 Quality based considerations for similar biologic

7.3.1 Analytical methods

7.3.2 Product characterization

i. Structural and Physicochemical Properties

ii. Biological Activity

iii. Immunological Properties

iv. Purity and Impurities

7.3.3 Specifications

7.3.4 Stability

7.4 Quality Comparability Study

7.5 Data Requirements for Preclinical Studies

7.5.1 Prerequisite before Conducting Preclinical Studies

7.5.2 Preclinical Studies (Pharmacodynamic and Toxicology Studies)

i. Pharmacodynamic Studies

ii. Toxicological Studies

7.6 Immune Responses in Animals

7.7 Data Requirements for Clinical Trial Application

7.7.1 Pharmacokinetic (PK) Studies

7.7.2 Single Dose Comparative PK Studies

7.7.3 Multiple Dose Comparative PK Studies

7.8 Pharmacodynamic Studies

7.9 Confirmatory Safety and efficacy Study

7.9.1 Waiver of safety and efficacy study

7.9.2 Non-comparative safety and efficacy study

8.0 Safety and Immunogenicity Data

8.1 Extrapolation of Efficacy and Safety Data to Other Indications

8.2. Data Requirements for Market Authorization Application

8.3 Post-Market Data for Similar Biologic

i Pharmacovigilance Plan

ii Adverse Drug Reaction (ADR) Reporting

iii Post Marketing studies (Phase IV Study)

8. APPLICATION FORMS FOR BIOSIMILAR DRUGS

Table: 1 Application forms for Biosimilar Drugs

Stage	Agency involved	Application	Approval
Manufacturing License for test, analysis and examination	State FDA / CDSCO	Form 30	Form 29
Preclinical studies permission	RCGM	Form C3	Form C4
Submission of Preclinical study report	RCGM	Form C5	Form C6
Clinical Trial	CDSCO	Form 44	Permission letter
Manufacturing and Marketing permission	CDSCO	Form 44	Form 45/46 (finished products)
Manufacturing License	State FDA/ CDSCO	Form 27D	Form 28D
Registration and Import License	CDSCO	Form 40/ Form 8	Form 41/Form 10

Table: 2 'Similar biologics' approved and marketed in India

Product name*	Active substance	Therapeutic area*	Approval/ launch date in India#	Company
AbcixiRel	abciximab	Angina, Cardiac ischemia	23 Apr 2013	Reliance Life Sciences
Actorise	darbepoetinalfa	Anaemia, Cancer, Chronic kidney failure	6 Jan 2014 (7)	Cipla/Hetero
Adfrar	adalimumab	Ankylosing spondylitis, Plaque psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis	11 Jan 2016	Torrent Pharmaceuticals
Bevacirel	bevacizumab	Colorectal cancer	10Jun 2016	Reliance Life Sciences (Lupin)
Biovac-B	hepatitis B vaccine	Hepatitis B	2000	Wockhardt
Cizumab	bevacizumab	Colorectal cancer	27 Jun 2016	Hetero
Cresp	darbepoetinalfa	Anaemia, Cancer, Chronic kidney failure	23 Mar 2010	Dr. Reddy's Laboratories
Darbatitor	darbepoetinalfa	Anaemia, Cancer, Chronic kidney failure	2014	Torrent Pharmaceuticals

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 minimized.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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