Invited Article

Similar Biologics: Regulatory Prospective in India

A. Ramkishan[1]*, Rajappan[2], Fahim Khan[3]

[1]Deputy Drugs Controller (India), [2]Drugs Inspector, [3]Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health and family Welfare, Govt. of India, Kotla Road, FDA Bhawan, New Delhi.

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A. Ramkishan

Corresponding Author:
A. Ramkishan
Deputy Drugs Controller (India),
Directorate General of Health Services,
Ministry of Health and family Welfare,
Govt. of India, Kotla Road,
FDA Bhawan, New Delhi
India

INTRODUCTION

The development and utilization of Biotechnology-derived therapeutic products namely, recombinant DNA derived products emerges as the fastest-growing segment in the pharmaceutical market. These products are large molecular weight and structurally complex molecules that are produced in living cells through genetic engineering. Biotechnology-derived therapeutic products are being developed over the past three decades and are under patent protection. The high cost of these therapeutic products has become a key issue in the battle concerning ever-increasing healthcare costs. The expiry of patent protection for biotechnology-derived therapeutic products of innovator origin has led to the development of Similar Biologics in India. Maintaining rapid as well as environmentally sustainable growth remains an important and achievable goal for India. In this concern, to meet unmet need and to append Make in India concept, pharmaceutical industry developed alternative similar biologics.

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. Similar Biologics also known as biosimilars, similar biological medicinal products, subsequent entry biological, second entry biological, biocomparable, biogenerics, multisource products, and off-patent biotech products as synonyms.

- Similar Biologics may not be treated as generic; as these are larger and more complicated than chemical drugs, due to the complexity of biotechnology derived therapeutic products the generic approach is scientifically not appropriate for Similar Biologics.
- **Current Global Biopharmaceuticals market size: ~200 Billion (USD)**
- Current Indian Biopharmaceuticals market size (2017): ~0.7 Billion (USD)
- Expected Indian Biopharmaceuticals market size (2025): ~2.5 Billion (USD)
- The Indian Biopharmaceuticals business is growing by 16% CAGR
- Indian manufacturers also marketing their Biotech products in Domestic, EMB and Global markets.
- **Regulatory bodies involved in Biosimilars approval in India**
- **RCGM- Review Committee for Genetic Manipulation**

- Under DBT, Ministry of Science and Technology
- Monitors & approval of clone development (GMO)
- Approval of Preclinical studies
- **GEAC- Genetic Engineering Advisory Committee**
- Under Ministry of Environment
- Environmental approval of products with Live modified organism
- **DCG (I)- Drug Controller General of India**
- Under Ministry of Health
- Monitors product safety and efficacy
- Approval for Clinical, Mfg. and Mkt. approval for drugs
- **NIB- National Institute of Biologics**
- Under Ministry of Health
- Development of Monographs and Reference Standards
- Testing of novel products before marketing the products
- Testing of every batch of plasma products and vaccines
- **FDCA- Food & Drugs Control Administration**
- State govt. body, Under Ministry of Health of respective states
- Approves plant, manufacturing & ensures cGMP
- Before carrying out clinical trials the firm has to submit Pre-clinical studies data to RCGM.
- After getting approval from RCGM, firm has to approach O/o DCG (I) for carrying out Clinical Trials in Human Beings.
- The firm has to submit NOC from RCGM and application in Form-44 along with requisite Fees as relevant data pertaining to similar biologics to CDSCO for clinical trial NOC.
- The said proposals of Biosimilar products along with pre-clinical data are to be discussed in subject expert committee (SEC) for necessary clinical trial permission.
- **Revision of Guidelines on Similar Biologics: 2012**
- **Need for Guidelines**
- Biologics are complex proteins.
- Manufactured by r-DNA technology,
- Are different than chemical drugs,
- Requiring advanced development and evaluation processes,
- Therefore, separate guidelines are needed. This is consistent with the approach being taken by all major drug regulatory authorities.
- Rule 122E of Drugs and Cosmetics Act 1940 specified that all the Biologicals are new drugs. Therefore, CDSCO approves the Biosimilars in India.
- **Guidelines on Similar Biologics, 2012: Key Points**
- Guidelines were prepared, finalized and uploaded in the website of CDSCO in Oct., 2012
- Elucidated the regulatory requirements for marketing authorization of Similar Biologic Products in India
- Prepared by DBT and CDSCO in consultation with various stakeholders and experts from Institutions like CDRI (Lucknow), PGIMER (Chandigarh), IIT Delhi, NIN (Hyderabad), IISc (Bangalore) etc.
- During the discussion of the 2012 guidelines preparation, it was anticipated by the group of experts that there would need for on-going review and revisions from time to time.
- **Rationale for Revision**
- The changes were made intended to establish a robust platform that will facilitate the development of high quality products and create increased alignment between the similar biologics regulations in India and global developments.
- The changes were made intended to deliver a clear and precise development pathway for the

approval of Similar Biologics product, which in turn will have a significant impact on the healthcare related to these products in India.

- The broad framework of the guidelines remains unchanged. However, the revision seek to enhance the scientific utility of the guidelines to ensure robust quality and clinical evaluations by explicitly -
- Defining similar biologics,
- Identifying critical and key Quality Attributes for establishing similarity,
- Specifying lower limits of minimum sample size for clinical evaluations,
- Making phaseIV safety evaluations compulsory and specifying lower limits of minimum sample size for it,
- Recognizing innovators' product as Reference Biologic (approved in ICH countries)
- Enabling parallel submission of applications to CDSCO and RCGM, DBT
- Incorporating procedural simplification
- Enumerating the applicability /scope of Guideline
- Clarifying on key technical terms and providing additional detail regarding specific technical matters based on

  (1) evolving global regulatory landscape and

  (2) the experience in India till date
- **Key revisions: Technical Matters**
- More detailed guidance and specific revisions were made in three distinct areas that are fundamental to the regulation of this class of complex products:
- Approach to the quality comparability study
- A specific section on the Quality Comparability Study has been added that explicitly defines a class of quality attributes – Critical Quality Attributes (CQAs) – where the proposed Similar Biologic has to be **within the range** that is established based on the Reference Biologic. This establishes a framework for product similarity that can be applied across all approved Similar Biologics and is consistent with the approach that the EMA and USFDA have taken.
- In addition to CQAs, the revised guidelines also define Key Quality Attributes(KQAs) which define all other parameters that need to be wellcontrolled to ensure the safety and consistency of the product.
- This approach to the classification of quality attributes, establishes a solid foundation on which the remainder of the development program for a Similar Biologic can be built. In the future, it will facilitate the development of productspecific guidelines that will help establish the expectations for high quality Similar Biologics.
- Pre-approval clinical evaluation with respect to safety and efficacy
- Revised guidelines require robust design of a comparative safety and efficacy study with the explicit requirement of not less than hundred evaluable patients on the test arm as per Indian GCP guidelines;
- This sets a minimum bar on the pre-approval data that needs to be gathered in a controlled clinical setting.
- Combined with the increased emphasis on product similarity and the existing requirements for pre-clinical and PK/PD studies this establishes a minimum bar for all future Similar Biologic approvals in the Country
- Post-marketing safety evaluation using Phase IV studies
- In addition, there has also been a significant addition to the post approval expectation of **Phase IV safety study** in more than two hundred evaluable patients, to create a minimum safety database of at least three hundred patients treated in a controlled setting for each approved Similar Biologic.
- This represents a **significant enhancement** to the scope of the safety database that will be available

to the regulatory agency and is consistent with the expectations of key global regulatory agencies.

- Taken together, these Revised guidelines significantly enhance the safety data that will now be **mandatory** for all manufacturers of Similar Biologics
- **Summary of Key Changes in Revised Guidelines: Section wise**

1. Introduction: Definition of Similar Biologic product provided –

"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".

1. **Background & Objectives: No changes.**
2. **Applicable Regulations and Guidelines: No changes**

Reference to Guidelines on Similar Biologics, 2012 added.

Scope: Requirements of a Reference Biologic have been revised:

2012 Guideline: Reference Biologic should have been licensed and marketed for at least four years in an ICH country, If not authorised in India.

Revision Made: Reference Biologic should have been approved/licensed in an ICH country, If not authorised in India.

This is to be considered in light of the full pre-clinical and clinical evaluation expected for a Similar Biologic

Principles for the development of Similar Biologics

- **Selection of reference biologic: No change** except for need for innovators product approved from ICH
- **Manufacturing process: No changes -** Molecular biology, cells, gene, fermentation, purifications aspects
- **Quality based considerations for similar biologics:** No changes Analytical methods, product characterization, specifications, stability studies

Quality Comparability Study:

- Now defines **Critical Quality Attributes** (CQAs), **Key Quality Attributes** (KQAs)
  - **CQAs:** Attributes for Similar Biologic has to be within the range that is established based on the Reference Biologic.
  - **KQAs:** Attributes for similar biologic has to be well controlled to ensure the consistency of product.
  - Analytical tests required for a comprehensive quality comparability exercise of critical and key quality attributes
- **Data requirement for Preclinical Studies:**
- **Procedural Simplification:**
- Post availability of toxicity study report, Clinical Trial Application to DCG(I) and toxicity study report to RCGM can be filed in parallel. However, DCG(I) will issue Clinical Trial NOC only upon clearance from RCGM.
- **Data requirements for Clinical Trial Application:**
- **2012 Guidance:** No guidance on minimum Phase III sample size provided
- **Revised Guidelines:** A clear expectation of a comparative safety and efficacy study with the explicit requirement of a not less than hundred evaluable subjects on the test arm; this sets a minimum bar on the pre-approval data to establish comparable efficacy.
- A protocol for a post marketing Phase IV open label, single arm safety study in not less than twohundred subjects on the Similar Biologic.
- This additional safety data will result in a robust safety database (100+200=300) that will help establish the safety of the proposed Similar Biologic.
- **Data requirements for Marketing Authorization Application:**
- The package insert of the Similar Biologic shall be based on data generated by the manufacturer or

from verifiable publicly available data on the Reference Biologic.

Post-market data for Similar Biologics:

- Pharmacovigilance Plan and Adverse Drug Reaction (ADR) Reporting : **no change**
- Post Marketing Studies (PMS): Addition of mandatory Phase IV safety study with more than 200 patients.

Application Forms: Additional forms included (RCGM).

Archiving of Data: Expectation for the manufacturer to establish SOP for data archival as well as sample retention.

Applicability: 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.

Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India is the Apex national regulatory authority in India that evaluates safety, efficacy and quality of drugs including Similar Biologics. Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India through Review Committee on Genetic Manipulation (RCGM) is responsible for overseeing the developmental and preclinical evaluation of Biotechnology-derived therapeutic products. The "Guidelines on Similar Biologics" prepared by both CDSCO and DBT to lay down the regulatory pathway for a Similar Biologic claiming to be similar to an already approvedinnovator product in the year 2012.During the preparation of Guidelines, it wasanticipated that there would need for ongoing review and revision from time to time.

The existing guidelines was revisedand implemented in the year 2016 which is made publicly available in CDSCO website. The revised guideline was prepared in consultation with Stakeholders and based on the real experiences to address the challenges faced during the previous years.

These guidelines not only addresses the regulatory pathway regarding manufacturing process and safety, efficacy and quality aspects for Similar Biologics, but also addresses the pre•market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for Similar Biologics.

Salient features of revised guidelines of Similar Biologics 2016

The changes made in the current guideline are intended to establish a robust platform that will facilitate the development of high quality products and create increased alignment between the Similar Biologics regulations in India and in global development.The revisions made are intended to deliver a clear and precise development pathway for the approval of Similar Biologics product, which in turn will have a significant impact on the healthcare related to these products in India.

The broad framework of the guidelines remains unchanged. However, the revision made to enhance the scientific utility of the new guidelines 2016 to ensure robust quality and clinical evaluations of bio-similars by explicitly;

- Defining Similar Biologics,
- Identifying Critical and Key Quality Attributes (CQA & KQA) for establishing similarity,
- Specifying lower limits of minimum sample size (100 patients) for clinical evaluations,
- Making phase IV safety evaluations compulsory (200 subjects),
- Recognizing innovators product as Reference Biologic (approved in ICH countries).
- Enabling parallel submission of applications to CDSCO and RCGM, DBT.
- Incorporating procedural simplification.
- Enumerating the applicability /scope of Guideline.
- Clarifying on key technical terms and providing additional detail regarding specific technical matters based on evolving global regulatory landscape and the experience in India till date.

More detailed guidance and specific revisions are made in three distinct areas that are fundamental to the regulation of this class of complex products:

1) Approach to the quality comparability study.

2) Pre-approval clinical evaluation with respect to safety and efficacy

3) Post-marketing safety evaluation using Phase IV studies

Approach to the quality comparability study:

A specific section on the Quality Comparability Study has been added that explicitly defines a class of quality attributes – Critical Quality Attributes (CQAs) – where the Similar Biologic has to be within the range that is established based on the Reference Biologic. This establishes a framework for product similarity that can be applied across all approved Similar Biologics and is consistent with the approach that the EMA and USFDA have taken. In addition to CQAs, the revised guidelines also define Key Quality Attributes(KQAs) which define all other parameters that need to be well-controlled to ensure the safety and consistency of the product.

This approach to the classification of quality attributes, establishes a solid foundation on which the remainder of the development program for a Similar Biologic can be built. In the future, it will facilitate the development of product-specific guidelines that will help establish the expectations for high quality Similar Biologics.

Pre-approval evaluation with respect to Safety and Efficacy

Proposed guidelines require robust design of a comparative safety and efficacy study with the explicit requirement of not less than hundred evaluable patients on the test arm as per Indian Good Clinical Practice (GCP) guidelines. This sets a minimum bar on the pre-approval data that needs to be gathered in a controlled clinical setting. Combined with the increased emphasis on product similarity and the existing requirements for preclinical and PK/PD studies this establishes a minimum bar for all future Similar Biologic **approvals in the Country.**

Post-marketing safety evaluation using Phase IV studies

There has also been a significant addition to the post approval expectation of Phase IV safety study in more than two hundred evaluablepatients, to create a minimum safety database of at least three hundred patients treated in a controlled setting for each approved Similar Biologic.

This represents a significant enhancement to the scope of the safety database that will be available to the regulatory agency and is consistent with the expectations of key global regulatory agencies.

These guidelines are for the guidance of all stakeholders and are not meant to substitute or rephrase the Rules made under Drugs and Cosmetics Act, 1940 and Rules, 1945 or any other relevant Acts in this concern.

SWOT Analysis of Biopharmaceutical products:

Strengths:

- Trained manpower availability in India
- Proven credentials in GMP
- Favourable ecosystem
- Developed Bio-similar industry & guidance

Opportunity:

- Very few countries are in Manufacturing
- Huge market in India and emerging markets
- Huge demand supply gap
- Several biotech products going off patent
- Revenue for ecosystem as well
- Know-how to develop Novel biologics

Weakness:

Less Exposure of advance requirements for US and EUEffective systems (Cold chain / Pharmacovigilance).

Threat:

- **Chinese and Latin America manufacturers (Govt. backing)**
- **Huge competition since 2010 (several**

innovators including Amgen, Pfizer investing in Biosimilars)

- **High competition - Low price – low profit (like Pharma Generics)**

Several challenges exist for Similar Biologics

Market – Price control, Competition

Physician / Doctors – Key Opinion leaders, Acceptability

Patients – Affordability - Price, Patients groups

NGOs & Innovator companies – Court cases

Product life – Novel biologics and pharma drugs

Initiatives required addressing Challenges

Manpower

- Manpower required from several disciplines
- Skilled and Trained manpower is required
- Industrial Biotech trainings should be geared towards Similar Biologics
- Projects at universities should be in applied research
- Academic institute should tie-up with Industry for routine work and train students

Reference Biologics

- Several hundred units of innovator product is required during development for Product Comparability
- Relaxation in custom duties /other duties / taxes can reduce the cost burden for development of Similar Biologics

Testing Laboratories

- Development of advanced analytical development labs to characterize the similar Biologics

Proper Guidelines and Pharmacopoeial Monographs

- Establish product specific product development guidelines – Harmonizing the regulatory path for every company
- Development of Pharmacopoeial monograph and reference standards to harmonize the quality standards

Majority of the Hurdles or the challenges can be addressed by having a Streamlined Regulatory framework

Recent Updates – Research and Development

- For undertaking research work and CTs on vaccines and r-DNA products, the manufacturing "No Objection Certificate" (NOC) for Form 29 requirement from the CDSCO is no longer required and firms can now directly approach the state FDA office for license without the NOC from Delhi office.
- Moreover, practice of prior joint inspection is also discontinuing.
- The validity of the manufacturing test-license (issued in Form 29) and import test license (issued in Form 11) has been extended from one year to three years.

It has enhanced the R&D capabilities of Industries and Academia

- The respective site Ethics Committee (EC) can approve request for adding new CT sites and for new investigators in a CT without CDSCO's approval as long as the EC conducts "due diligence".
- The requirement of audio-video recording of informed consent process (which was mandatory for all CTs in the past) has been relaxed.
- Audio-video recording has now been made mandatory only for cases where vulnerable population is involved and in case of CTs being done with a new chemical entity or new molecular entity.

This has reduced the burden on CRO and sponsors to apply and get separate approvals from the CDSCO

Digitalization

- To improve transparency, accountability, and efficiency in processing of different types of applications and their monitoring, the CDSCO has

taken initiative for making several submissions online through SUGAM portal for different approvals in India.

- Some of the state FDA (Gujarat, Maharashtra) has also started online submissions.

This is in line with the GOI Digital India initiative and will certainly reduce the paper work and other formalities

Exports of Drugs:

- For export of unapproved r-DNA drugs and vaccines, firms seeking NOC to export the samples can now expect to get the NOC from CDSCO within 10 days of submission of requisite documents including a valid export order.
- RCGM
- For r-DNA derived drugs like insulin, monoclonal antibody, etc., application can now be filed in parallel to Review Committee on Genetic Manipulation (RCGM) and the CDSCO office for seeking approval to conduct CT. Both the agencies can independently start their review process and issue their respective approvals to the firm.
- Condition for taking RCGM permission to import recombinant cell lines for research and development or commercial purpose has been discontinued.

This has promoted the research based innovation environment in academic institutions and other biotech startups

- The Center has also created "Life Sciences Skill Development Council" in an effort to train and upgrade the skill sets of personnel employed in pharmaceutical manufacturing units.
- **The more skilled people will lead to provide better quality of the drugs**

Regulatory key persons for biological products

Central Drugs Standard Control organization (CDSCO) is headed by Dr. G. N. Singh, Drugs Controller General (India). Dr. V. G. Somani, Joint Drugs Controller (India) is responsible for overall supervision of regulatory procedures. Biological Division of CDSCO (HQ), functions under the supervision of Dr. A. Ramkishan, Deputy Drugs Controller (India) who is assisted by Assistant Drugs Controllers, Drugs Inspectors and Assistant Drugs Inspectors.

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