Frequently Asked Questions  
for  
Guidelines on Similar Biologics 2016: 
Regulatory requirements for Marketing Authorization in India

1. What is the Need and Objective of this Guideline?

With several companies venturing into similar biologics, a strong need was felt to streamline the regulatory process through a well defined set of guidelines for the authorization of similar biologics in India.

These guidelines would be of immense help to industry as well as regulatory agencies to become globally competitive and also provide safe, effective and affordable similar biologics in the country.

These guidelines has been developed by Joint efforts of members of task force set up by CDSCO (including industry members) and subcommittee of RCGM – DBT to ensure that consistent science based and data driven standards are applied in the approval process of similar biologics.

2. What is “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.

Such products are also referred as biosimilars, similar biotherapeutic products, subsequent entry biologics or follow on biologics in various countries.

3. What is the scope of the “Guidelines on Similar Biologics”?

These guidelines apply to similar biologics that contain well characterized proteins as their active substance, derived through modern biotechnological methods such as use of recombinant DNA technology. The demonstration of similarity depends upon detailed and comprehensive product characterization, preclinical and clinical studies carried out in comparison with a reference biologic.

4. Is Guideline on Similar Biologics applicable for both indigenously and imported developed similar biologics?

Yes, the guideline is applicable for similar biologics developed in India or imported into the country.

5. When will be the Guideline on Similar Biologics implemented?

The guideline will be implemented from XX.YY.ZZZZ. The application submitted before the implementation date will be evaluated based on previous regulatory norms.

6. Who regulates Similar Biologics in India?

Following three competent authorities are involved in the approval process of similar biologics in India.

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

- **Genetic Engineering Appraisal Committee (GEAC):** GEAC is responsible for review and approval of activities involving large scale use of genetically engineered organisms (also referred as living modified organisms) and products thereof in research and development, industrial production, environmental release and field applications.

- **Central Drugs Standard Control Organization (CDSCO):** CDSCO is responsible for the approval of new drugs. In the context of similar biologics, CDSCO is responsible for grant of import/export license, clinical trial approval and permission for marketing and manufacturing.
7. **How are Similar Biologics regulated in India?**

In India Similar Biologics are regulated at various stages of product development by several regulatory agencies.

The Biopharma product development starts with either clone development or clone import, for which permission is needed from RCGM. Similarly, application for “carry-out-research” approval is made to RCGM.

Form 29 license is obtained for manufacturing of product for the purpose of examination test and analysis, Form 29 is obtained from FDA after CDSCO and DCGI clearance.

After receiving above referred approvals from RCGM, DCGI and local FDA, the firm develops / imports the clone and initiates the analytical and process development activities. Once the process is frozen, three consistency batches are taken and product characterization is completed, the firm applies for approval to conduct preclinical toxicity studies to RCGM. The preclinical application is reviewed in RCGM meeting after which the approval is granted to the firm. After obtaining the approval, preclinical toxicity studies are conducted.

Once the preclinical studies are completed the firm applies for NOC for CT to RCGM.

Upon obtaining the NOC for CT from RCGM, the clinical trial application is made to DCGI in Form 44 as per CDSCO format for clinical trial application along with CT protocol, DCGI grants CT permission to the firm after review of the CT application and protocol.

After receiving CT permission from DCGI, the firm initiates the CT trial. Once the Clinical trial is completed, the firm applies for marketing approval to DCGI in Form 44 as per CDSCO application format for marketing authorization along with CT report. DCGI reviews the Marketing application and CT report, and grants marketing approval (Form 46A and Form 46) to the firm.

After obtaining marketing authorization permission (Form 46A and Form 46), the firm applies in Form 27D for Form 28D (Manufacturing License) to local FDA.

Once Form 28D is granted the firm launches the product in Indian market and after collecting required data the firm applies for WHO GMP certificate. Joint inspection is conducted after which WHO GMP certification is granted by Local FDA for the product in question.

8. **What are the key principles for developing Similar Biologics?**

Similar biologics are developed through sequential process to demonstrate the similarity by in quality, safety and efficacy attributes with reference biologic product.

9. **What is the basis of the Similar Biologics guideline?**

The basis of this guideline is thorough comparison of similar biologic with innovator product for demonstration of similar quality, safety and efficacy attributes.

EMEA guideline on similar biological medicinal products and WHO guideline on evaluation of similar biotherapeutic product are used as references to prepare the “Guideline on Similar Biologics”.

10. **What is a reference biologic?**

A reference biologic is an originator biological product approved in India or ICH countries used as the comparator for comparability studies with the similar biologic in order to show similarity in terms of safety, efficacy and quality. Only a product that was licensed on the basis of a full registration dossier can serve as reference biologic.

11. **Are comparative studies required as per Guideline on Similar Biologics?**

Yes, comparative studies are required to prove analytical similarity, non-clinical similarity and clinical similarity.
12. What are the key CMC components to be addressed as per Guideline on Similar Biologics?
Key CMC components to be addressed as per Guideline on Similar Biologics include clone development, fermentation process development, downstream process development, analytical method development, product characterization / quality biosimilarity, specification(s) and stability studies.

13. What are the tests required for Quality comparability?
The quality comparison between the similar biologic and the reference biologic should employ state-of-the-art analytical techniques, including the analytical methods that are sensitive enough to detect the possibilities of changes to the similar biologics. The category of tests include structural analysis (primary, secondary and tertiary structure), biological function, purity and impurities. The list of routine analytical tests to be included for quality comparability exercise is given in Annexure-2 of the Guideline on Similar Biologics.

14. Which Pre-Clinical studies are required as per Guideline on Similar Biologics?
Following studies are required for preclinical evaluation:
- In vitro and in vivo pharmacodynamic studies
- Repeated dose toxicity study (at least one such study)
- Study for evaluating immune response in animals

15. Which Clinical trials are required as per Guideline on Similar Biologics?
Following studies are required for clinical evaluation:
- Comparative pharmacokinetic (PK) studies
- Comparative pharmacodynamic (PD) studies
- Comparative confirmatory clinical safety and efficacy study (including the immunogenicity study)

The above studies can be done in parallel and wherever possible can also be combined.

However phase II is not required for similar biologic development as the similar biologic is supposed to use same dose, have same strengths and use same route of administration as reference biologic.

16. Can the extrapolation of indications possible as per Guideline on Similar Biologics?
Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if certain conditions are met like; similar mechanism of action, same receptor involved for all indication, established similarity in quality, pre-clinical and clinical studies (in one indication).

17. What are the post market authorization requirements as per Guideline on Similar Biologics?
The post market authorization requirements include pharmacovigilance including submission of Periodic Safety Update Reports (PSURs), adverse drug reaction (ADR) reporting and post marketing studies (PMS).

18. What are the key national regulations and guidelines applicable?
The similar biologics are regulated as per
- Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (and relevant amendments)
- 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:
  - Submission of Clinical Trial Application for Evaluating Safety and Efficacy
  - Requirements for permission of New Drugs Approval
  - Post approval changes in biological products; Quality, Safety and Efficacy Documents
  - Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011

19. What are the key international guidelines applicable?
ICH Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
ICH Q5B: Quality of Biotechnological Products: Analysis of The Expression Construct In Cells Used for Production of rDNA Derived Protein Products
ICH Q5D: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biological Products
ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
ICH Q5C: Stability Testing of Biotechnological/Biological Products
ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
ICH Q5C: Stability Testing of Biotechnological/Biological Products

20. Do the manufacturers or importers have to follow Mashelkar Committee report for development of similar biologics?
Yes, as per the similar biologic guideline, the manufacturers or importers have to follow Mashelkar Committee report for regulatory pathway (refer Annexure 1 of Similar Biologics guideline).

21. Whom do we contact for further details or queries?
Manufacturers can contact RCGM, Department of Biotechnology & Central Drugs Standard Control Organization. The details given below:

Department of Biotechnology
Ministry of Science and Technology
Block- 2 CGO complex, Lodhi road
New Delhi – 110003

Telephone:
Fax:
Email:

Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
Government of India
FDA Bhavan.
ITO, Kotla Road, New Delhi-110002

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