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A review on Regulatory guidelines for biologics in India

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INTRODUCTION:

The guidelines on similar biologics are setup by CDSCO & DBT for the regulatory pathway of similar biologic products. These guidelines direct the pathway for manufacturing process and quality aspects of similars biologics

Objective:

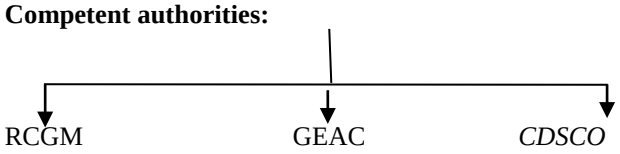
CDSCO (Central Drug Standard Control Organization) is a regulatory authority of India and which access and concentrates mainly on the safety and effectiveness of the drugs in the country. DBT (Department of Biotechnology) and RCGM (Review Committee of Genetic Manipulation) is accountable for the pre-clinical evaluation of recombinant biologics. Similar biologics are agreed below this pathway and which gives a clear idea to confirm the safety, quality and efficacy of the similar biologic product. The significant aim of this guideline is to authorize and comply with regulatory requirements for authorization of similar biologics in India.

Applicable Regulations and guidelines:

These biologics are regulated under the Drugs and Cosmetics Act 1945 and based on the regulations for the production, usage, import, export of micro-organisms genetically engineered organisms 1989.
Some of those guidelines are:

- Recombinant DNA safety guideline , 1990
- Guidelines for generating pre-clinical and clinical data for RDNA vaccines, 1999
- Guidelines and Handbook for Institutional Bio-safety committee
- CDSCO guidance for industry, 2008:
  a) Capitulation of CTA for Evaluating Safety and Efficacy
  b) Requirements for acceptance of New Drugs Approval
  c) Post approval changes in biological products: Quality, Safety and Efficacy Documents
  d) Establishing the requirements of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products

Competent authorities:



a) Review Committee on Genetic Manipulation (RCGM)
   - ✓ The main role is in the Department of Biotechnology (DBT)
   - ✓ Responsible for import and export for research and development and evaluation of data.

b) Genetic Engineering Appraisal Committee (GEAC)
   - ✓ It works below the ministry of environment and forests as statutory
   - ✓ Body of evaluating and approving the genetically micro-organisms in large scale used for the evolution and research, environment investigation.

c) Central Drug Standard Control Organization(CDSCO)
   - ✓ Comes under the control of DCGI
   - ✓ The ultimate role is approving new drugs, and for grant of import/export license, clinical trial approval and authorization for marketing and manufacturing.
   - ✓ Also SFDA and CDSCO issue a license to manufacture (or) produce similar biologics in India.

Scope:

These guidelines can also be used to the well determined proteins with their functionate substance existed through DNA recombinant technology. The similar biologics are formulated with reference biologic product that has approved in india.If it is not licensed in india, it should have marketed and allowed for minimum of 4 years with sufficient and significant safety and efficacy data. The similar biologics can be examined only when it proves the same quality attributes that of reference biologic product.

Principle involved in similar biologics:

It is mandatory to prove the similar biologicals meet the acknowledged levels of the reference biologic products to make sure the public health. The consistency of production process may vary depends on reference biologic.

i) <u>Selection of reference biologic:</u>
It is necessary for development of similar biologic. It depends upon the DBT & CDSCO. The reference biologic should be

- Licensed in India and should be discoverer product.
- If it is not licensed in India, it should be widely distributed for minimum of 4 years in accordance with their regulatory guidelines.
- The same reference biologic product should be utilized to fill the complete of the whole study

ii) Manufacturing process:

This process should be stable and strong. In case if the host cell line is used for the manufacture of reference biologic, the same should be used for the similar biologic product. In order to initiate and characterize the cell banks the guidelines framed by the ICH can be used such as Q5A,Q5B,Q5D guidelines are preferred.

Some of the outcomes are listed below:

a) Molecular biologic considerations:

The information based on the host cell cultures, vectors, gene sequences, promoters are used in the manufacturing of similar biologics. If there is any up-right translational manufacturing such as glycoylation, oxidation should be detailed.

b) Fermentation process development:

Three batches should carry out the replicate fermentation

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Fermentation process must be operated in a controlled environment

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Factors such as PH, temperature and dissolved oxygen should be noted

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Production should be replicatable and scalable.

Data should remain sustained for all the batches.

c) Downstream Process development:

- It is used for protein purification processes.
- The functioning step during purification to recovery state should be described briefly.
- It should explain the refolding process, particular activity at various doses, Dose response curve.
- There should be a continuous recovery in three batches.

In case of submitting the clinical trial application. A proper GMP should be maintained during the manufacture and production process. The data includes

i) Detailed description of drug substance
ii) Critical quality attributes of product
iii) Critical process parameters
iv) Stability data
v) Comparability of product manufactured at clinical scale against reference biologics.
vi) Data from consistency batches and /or process validation batches as applicable.

iii) Quality based considerations for similar biologics

a) Analytical methods:

- Selected based upon the critical quality attributes of the product.eg: Multiple, orthogonal methods are preferred for characterization.
- Methods used to measure those attributes are batch release, stability studies and in-process controls are checked according to the ICH guidelines, ICH Q2,Q5C,Q6B

b) Product characterization:

The similar biologic product should include the characterization and properties of physicochemical, biological, immunological properties, functional assays, purity, contamination and strength.

i) Structural and Physicochemical properties:

It includes the determination of primary and higher order structure of products along with the important physicochemical properties. It also includes the accuracy and the precision.

ii) Biological activity:

The biological products have many number of biotic activity. The product should initiate the mechanism of action and clinical effects. It should be matched to that of standards if not it should be marked as per ICH guidelines.

iii) Immunological properties:

The recombinant biologics may influence the associated impurities and post translational modifications of the product. It may also examine the factors such as specificity, affinity, binding strength

iv) Purity and impurities:

Some of the analytical procedures can also be done.

- Product allied variants: glycoforms, isomers
- Product allied impurities: aggregated products
- Host-cell related impurities
- Process related impurities

c) Specifications:

Specifications methods are not more same as that of analytical methods. Acceptance limits are set based on the instance of the biologic data.

d) Stability:

To regulate the shelf-life of the product. This is connected on containers and conditions based on the ICH guidelines ICH Q5C

iv) Quality Comparability study:

Quality comparison is analyzed between the similar biologic and reference biologic. The complete dossier should be given as per CDSCO guidance for industry 2008.Three batches are subjected for demonstrating the consistency of the quality system.

Data requirements for pre-clinical studies:

A) The applicant should present the data created along with pre-clinical study protocols to RCGM for acquiring permission. Toxicology studies should start once, the permission from RCGM. Some of the information's are required such as:

- Information on drug administration, dosage, absorption and eliminate rate
- Mechanism of Action
- Available toxicity data.

B) Pre-clinical studies:

It is performed before the clinical studies. It is necessary for the contrasting the similar biologic and reference biologic. Factors such as dosage form, strength and route of administration should be justified.

i) Pharmacodynamic studies:

In-vitro: Comparative tests and reference biologics.eg: Cell proliferation assay.

In-vivo: Assessment of biological and Pharmacodynamic activity.

ii) Toxicological studies:

In in vivo toxicity studies, one repeat dose toxicity must be performed, during this study the animal utilized for this study should give a proper justification for sacrificing. These studies are performed based on the two species i.e rodent and non-rodent species as stated by the schedule Y with permission on RCGM . The dose toxicity testing will consists of:

- Historical control
- Vehicle control
- Vehicle control for recovery groups
- 1X reference biologic for study duration
- 5X high dose similar biologic.

The protocol and the study reports should consists of :

- Methodology before euthanasia
- Events directly after euthanasia
- Biochemical parameters
- Hematology
- Statistical methods.

The final report of study should consists of

- RCGM approval of protocol
- IBSC approval of report
- IAEC approval
- QA statement
- Animal feed
- Discussion on the results
- Conclusion

C) Immune response in animals:

Antibody response in animals is differentiated with reference biologic that of a similar biologic. The serum samples are experimented for reaction to host cell proteins. After the finalization of pre-clinical studies, the reports are submitted to RCGM for review and consideration.

Data requirements for clinical trial application:

The applicants have to submit the application for the conduct of clinical trial as per CDSCO 2008 guidance.

a) Pharmacokinetic studies:

These studies are conducted in health volunteers to contrast between the similar biologic and reference biologic. Some of the factors have been considered.

- Half life
- Linearity to pharmacokinetic parameters
- Conditions and diseases to be treated
- Route of administration
- Indications.

Design considerations:

- Single dose, comparative PK studies
- Parallel arm
- Cross-over

b) Pharmacodynamic studies:

These studies are also contrast in nature. Design considerations involved here are:

- Comparative
- Parallel arm (or) cross over

Pharmacodynamic studies are conducted only in healthy animals. The response/efficacy of the instance biologic should be same to that in order to rationalize the design. It is a section of phase III clinical trials.

c) Confirmatory safety and efficacy study:

This is mandatory for all the similar biologics in order to demonstrate its safety and efficacy. Well matched clinical compatibility and end points should be justified according to their design. If trials are not essential it should be given clarification and applicants should submit their application according to CDSCO. It makes sure a difference between similar biologic and reference biologic

The clinical trials are confirmed based on the conditions below:

1. Systemic and functional comparability of similar and reference biologic
2. Comparable
3. Post-marketing

d) Safety and immunogenicity data:

Evaluation based on pre-clinical trials and post clinical data which presents with the complete set of safety and immunogenicity data.

Data requirements for marketing authorization application:

The applicant should present their application according to the CDSCO guidance document as per 2008.The report and protocol of phase III clinical trial is mandatory. The comparability test between the similar and reference biologic should also be attached.

Post-market data for similar biologics:

The similar biologic is same that of a reference biologic and it is necessary to submit the risk assessment plan.

The plan involves:

a) Pharmacovigilance plan:

The plan is like it is necessary to submit the PSURs (Periodic Safety Update Reports) and should be submitted every six month after the submission of application.

b) ADR reporting:

Serious adverse events should be reported within 15 days as per scheduleY

c) Post-marketing studies:

The post-marketing studies are noted on the pharmacovigilance plan and updated studies should be submitted to CDSCO.

CONCLUSION:

Since the bio-similars and biologically similar products are emerging and which has a very wide scope in future in generating of medicines accordingly to similar biologic product. It should be helpful in manufacturing the better products according to the CDSCO guidelines. Now there is a changes in guidelines (i.e) amendments of a new plans such as pharmacovigilance plan, post-marketing studies.

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