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Review Article

**Regulatory aspects for Biologic product licensing in India**

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Abstract

Biologics are the medicinal/ therapeutic/ diagnostic/ preventive preparations composed or derived from living organisms and their spin-off for human use. They include serums, vaccines, antitoxins, blood, antigens and blood components, gene therapy, tissues etc. Biotechnology is used as a unique approach in manufacturing such medicinal agents. The Indian National regulatory authority (CDSCO) is the body that is responsible for manufacturing and import of biological products in India. Biotechnology provides innovative solutions to medical field with more than 200 biologic medicines and vaccines. These developments benefits millions of patients worldwide and more than 600 products under development. At present these products can also be produced by manufacturers other than the innovator, with the expiry of some of patents. These new biotechnological medicines commonly referred to as 'similar biologics' offer a major opportunity to provide greater access to reasonable healthcare for several lifesaving medicines. India has emerged as one of the leading providers to the world market for 'Biosimilars'. These may be considered to be very essential economical and therapeutical element for the pharmaceutical market in India. The Indian National Regulatory Authority is considered to be responsible for evaluating safety, efficacy and quality of all pharmaceuticals in India. The Department of Biotechnology in India is the department that governs the development, pre-clinical studies of all Biologicals.

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E-mail address: sanjeevpkmskm@gmail.com (Sanjeev Kumar Maurya).**1. Introduction**

The annual turnover of pharmaceutical industries in India is valued at US\$ more than 30 Bn in 2017. India's total Pharmaceutical industries are approaching to more extensive at a CAGR of 22.4 % over 2015-2020 to reach at US\$ 17.27 Bn in 2017-2018 and is expected to reach US\$ 20 Bn by 2020 (1). The biotech Industries in India is of size of rupees 25,165 crore approximately as per the data available, and out of which 63% of revenue is contributed by biopharmaceuticals sector, i.e. rupees 15,853 crore (1). The Biopharma sector's strength is the evident from the fact that Indian Biopharma companies are not only meeting the domestic requirements but also exporting their products to more than 150 countries. Indian vaccine industry has occupied an important niche in the manufacturing of EPI vaccines in the last decade and is one of the major suppliers to United Nations (UN) agencies of pre-qualified vaccines. This is a testament of impeccable credentials with respect to safety, quality and efficacy of the vaccines produced by Indian companies

(1). Now, the Indian biopharma companies are venturing into the areas of development of tetravalent dengue vaccine, oral cervical cancer vaccine including vaccines for neglected tropical diseases, such as chikungunya and kala-azar. These regulations plays very essential role in the growth of this sector.

Regulation of Biologicals

The manufacturing and import of biologicals are being regulated under the provisions of Drugs and Cosmetic Act 1940 and rules 1945. The manufacture and import of all biologicals without a license is an offence under the drug and cosmetic act 1940 (1). In India, biologicals include both the vaccines and as well the recombinant DNA products that are considered as new drugs as per the drug and cosmetic rules 1945. All these products will require new drug approval from the central licensing authority called as DCGI. Biologicals in India include both vaccines as well as recombinant DNA products which are considered as new drugs as per Drugs and Cosmetic Rules

1945. The drugs and cosmetic rules provide specific information to be furnished by the applicant for approval of new drug as specified in Form 44 with schedule Y (1). The schedule Y gives detailed guidelines on conduct of preclinical and clinical studies and data required in respect of manufacture and quality control. As per Indian guideline, one repeat dose toxicity study is sufficient to demonstrate comparability in relevant animal model. Clinical studies phase 3 is required as per Indian guidelines for approval of biologicals. Generally for vaccine, comparative phase 3 clinical trial in healthy volunteers is required (1).

Quality Control of Biologicals

The test or analysis of biological requires highly specialized facilities and expertise supported by an animal facility. There are two labs at the national level, i.e. (a) Central Drug Laboratory, Kasauli, (b) National Institute of Biologicals, Noida. The quality control testing and release of lot is carried out at Central Drug Laboratory, Kasauli whereas the National Institute of Biologicals is notified as central drugs laboratory under the drug and cosmetic act and rules for the various biologicals. The central drug laboratory, kasauli, does the quality control testing and lot release for vaccines whereas National Institute of Biologicals is notified as Central Drugs Laboratory under Drugs and Cosmetic Act and Rules for different biologicals, i.e. (a) blood groupings reagents, (b) diagnostic kits, (c) blood products- human albumin, human coagulation factor.

Applicable Guidelines (3)

The guideline for the biological in India is as following:

- Guidelines for Recombinant DNA safety, 1990
- Creating and Generating clinical and pre-clinical database for recombinant DNA all vaccines and diagnostics and other biologicals guidelines, 1999
- Guidelines and Handbook of IBCs, 2011
- CDSCO guidance for industry, 2008
- Application for Clinical trial submission for evaluation of efficacy and safety
- Permission Conditions of New Drug Approvals
- Biological products post approval changes: quality, efficacy, safety document
- Information of Quality for submission of drugs for New Drug Approval: biotechnologic or biologic products

Manufacturing Process of Biologicals (3)

The manufacturing of biologicals must be highly consistent. The data required including brief of manufacturing activity by characterization and development of cell banks, stabilization of clones, excipients, formulation, and purification. Also the result on product characterization is following as:

- Considerations for molecular biology
- Process development - Fermentation
- Process development - Downstream

Quality Comparability Study

This study is carried out between branded biologic and similar biologic. The applicant must submit a dossier of quality as per CDSCO guidelines for industry, 2008. The first three consecutive batches must be used that have been used for demonstration of consistency for the production purposes (3).

Clinical Trial Application for Biologicals (3)

Followings are requirements for the Biological clinical trial application:

1. **Pharmacokinetic studies:** This includes Absorption, Distribution, Metabolism and Excretion.
2. **Single dose pharmacokinetic studies:** Dose in Pharmacokinetic studies must be under therapeutic dose range for standard Biologic. Proper ratio for dose selection shall be provided. The administration route shall be that one where the sensitivity to analyse differences is largest. The size of sample must have statistical ratio and limits for comparability shall be defined and justified before for conducting of studies.
3. **Pharmacodynamic studies:** This includes the study of biochemical and physiological effects of drugs.
4. **Multiple dose studies:** These studies are required for a Similar Biologic which is used in a multiple dose regimen.
5. **Confirmatory safety:** The establishment of in-vitro, pre-clinical and Pharmacokinetic/ Pharmacodynamic Similarity as described in earlier section is important as robust, high quality processes, a comprehensive quality comparison and comparative preclinical and Pharmacokinetic /Pharmacodynamic studies help in demonstrating the Similarity of the Similar Biologic in these settings.
6. **Efficacy study:** Efficacy study is defined as the performance of an intervention under ideal and controlled circumstances.
7. **Immunogenicity studies:** Both the pre-approval and post-approval evaluation of safety is desired to be conducted for a Similar Biologic. Regarding pre-approval safety assessment, comparative pre-approval safety data including the immunogenicity data is required for all Similar Biologicals including those for which confirmatory clinical trials have been waived.

Types of Application (3, 4)

If the reference biologicals are not authorized in India then it has to be registered and marketed for minimum of four years with all necessary safety and efficacy data.

Submissions of various applications forms to regulatory agencies are as follows:

Purpose	Agency involvement	Application forms	Approval forms
License of manufacturing for examination, tests and analysis	CDSCO	Form no. 30	Form no. 29
Permission for preclinical studies	RCGM	Form no. C3	Form no. C4
Submission report of preclinical study	RCGM	Form no. C5	Form no. C6
Conduction of clinical trials	CDCSO	Form no. 44	Letter of permission
Permission for manufacturing and marketing	CDSCO	Form no. 44	Form no. 45/46
License for import, registration	CDSCO	Form no. 40/8	Form no. 41/10
License for manufacturing	CDSCO	Form no. 27D	Form no. 28D

2. Data Required for the Application of Market Authorization

- For market authorization, application must be submitted by the applicant according to CDSCO norms and document for industry guidance, 2008
- The manufacturing for trading purposes are approved on a different level or with separate processes as compared to that are being used for trials of manufacturing phase 3 clinical batches (3, 5).

Post- Market Data Required for Biologicals

- **Pharmacovigilance or Drug Safety (PV):** It is the science of pharmacology relating to, detection, collection, assessment, monitoring and prevention of adverse effects.
- **Adverse Drug Reporting (ADR):** It is the reporting and analyzing of all the adverse events occurred after the administration of product.
- **Post Market Surveillance (PMS):** It is the practice of monitoring the safety of a pharmaceutical product after it has been released into the market (3, 5).

Data Required for Pre-clinical Studies (3, 5)

Followings are the data required for preclinical studies for biologicals:

Pre-Requisite before Conducting Pre-Clinical Studies

- **Information about the drug:** This includes identification, pharmacokinetic to dose, adverse effects and utilization.
- **Route of administration:** It is a path by which a drug is taken into the body. Commonly routes are oral and intravenous.
- **Absorption rate:** It is the rate at which the drug moves from intestinal tract into systemic circulation.

- **Elimination rate:** It is the rate at which the drug is eliminated out from the body.
- **Mode of administration:** Mode or routes can be taken into considerations on where the target of action is.
- **Mode of action:** How a drug produces its pharmacological actions into the body.

Pre-Clinical Studies

- **Pharmacodynamic studies:** It is the study of the biochemical and physiologic effects of drugs (especially pharmaceutical drugs).
- **Toxicology studies:** These are the studies used to assess the onset, severity, and duration of toxic effects.

Immune Responses in Animals

After all the successful assessment of the pre-clinical study reports, The Review Committee on Genetic Manipulation (RCGM) will guide the applicant to precede DCGI for conduction of clinical trials according to CDSCO guidelines.

Competent Authorities (4, 5)

All the competent authorities that are involved in the approval processes are as follows:

Institutional Biosafety 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.

Review Committee on Genetic Manipulation (RCGM)

RCGM is functioning by Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India. In the statement of Similar Biologics, RCGM will be 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 for preclinical assessment.

Genetic Engineering Appraisal Committee (GEAC)

This committee works under the Ministry of Environment and Forests (MoEF) as statutory body for review of applications and approval of activities where final drug product contains genetically modified organisms/ living modified organisms.

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.

The Current Regulatory System

The federal regulatory structure of India has been pestilence by the vintage problems of developing countries, including bureaucracy and corruption. Expanding bureaucracies have been dainty hard on biologic manufacturers in India, who must take approval from multiple states and district, and federal agencies for routine activities such as the importation of recombinant molecules and cell cultures for research purposes. In India, the state authorities are in-charge for licensing a drug maker's research and facilities for manufacturing (2). But, the Central Drugs Standard Control Organization (CDSCO) and the Drugs Controller General of India (DCGI) have been responsible for the approvals of pre-clinical, clinical trials, new drug applications, and the import of drugs. For biologicals, some supplementary approvals has been required by other offices and agencies, that includes the Genetic Engineering Approval Council (GEAC), Recombinant DNA Advisory Committee (RDAC), Review Committee on Genetic Manipulation (RCGM), Institutional Biosafety Committees (IBSC), State Biosafety Coordination Committees (SBCC), and the District Level Committees (DLC) (2). Probably, the worse problem has been the absence of state-level regulations in some areas. India's state drug regulatory authorities (DRAs) also lack the staff to defend their respective domains. These sorts of staffing problems, combined with their limited technical experience in regulatory issues, makes difficult situation. A

manufacturer that sets up operations in states where the regulatory inaccuracy and prosecutions are weakest, could then market their drugs in the rest of the country. One senior federal regulator in India mourns, "There are hardly any regulations or control over the mistakes or offences committed by the State DRA Officers who permit even the manufacture of banned or new [i.e., unapproved] drugs. India's regulatory environment usually affects every country that imports its drugs. Products that has been made in India recons for 20% of US FDA generic applications in 2006, up from only 7% in 2001 (2).

Tighter Manufacturing Rules

The government of India admit the needs for tighter regulatory standards. The Regulatory Officials declared tighter enforcement to international good clinical practice (GCP) and World Health Organization protocols. DCGI also affirm that it will initiate regular inspections of on-going clinical trials. More necessarily, the two regulatory initiatives have taken. The First is creation of National Biotechnology Regulatory Authority (NBRA), under Department of Biotechnology (DBT), as a part of India's long-term biotech sector development strategy. In the manufacturing area, though, the country has been tightening the rules and enforcement. A new regulation "Schedule M" of the Drug and Cosmetics Act has now specifies the good manufacturing practices (GMP) requirements for factory premises and materials. These requirements were designed after US FDA regulations, to improve the regulatory co-ordination between both the Indian and US regulators. The changes have not met with universal approval, however. Small-scale manufacturers in particular argue that although the new requirements will improve quality, the changes must have been phased in gradually. It took the FDA nearly 15 years to tooling or executing similar like programmes in the U.S (2).

Streamlining Approvals

India recently started to tackle its officials to promote drug development. To motivate future makers of bio generics, e.g., India's regulatory system has begun to issue and publish guidelines on biosimilars and the various requirements for getting approvals. In 2005; India's legislation enforces a revision to the persuade Drugs Control Act, clarifying their rules on clinical trials. Earlier, for example, Phase 3 clinical trials within India were authorised to begin only if all studies had been conducted in Western countries (2). Now, only Indian companies are authorised to conduct first-inhuman studies and involve substantial efforts to earn approvals. Ethics committee and DCGI reviews of applications are now occurs parallelly and taking not more than 14 weeks. Even so often, clinical trial sponsors speeding up this process by submitting the draft application to DCGI to have the clock ticking, and after then file more complete data weeks later.

3. Approval Process in India (5)

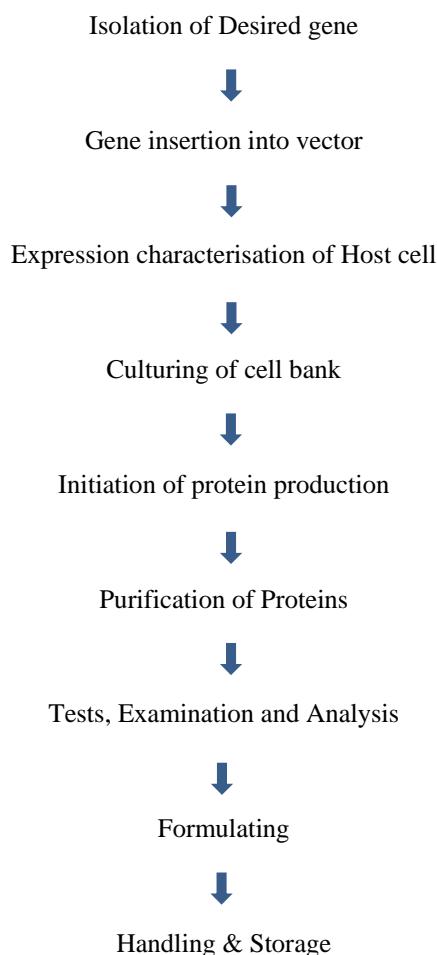
- Mandatory, transparent
 - Institutional Scientific Committee

- Ethics Committee (Institutional, National)
- Import permit of vaccines (DCGI) – MOH&FW
- National Regulatory Authority (DCGI) – MOH&FW
- Approval Committee for Genetic Engineering(Environment and Forest Ministry)

- Screening Committee by Health Ministry

Steps Involved in Development of Biologics

The steps that are involved in the development in the biologicals are as follows (4, 5):



4. Conclusion

After the study of Regulatory Aspects for Biologic Product Licensing in India, I have come to know about the various regulatory requirements, product licensing and different kinds of applicable forms that are necessary to taken into considerations for the biologic product manufacturing, import, marketing and sales in India.

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Conflict of interest

The authors declare that there is no conflict of interest.

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