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Regulatory requirements for approval of biological products as per CDSCO in Indian comparison with South Korea

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Abstract

Biologicals are restorative, therapeutic, analytic, preventive, arrangements created or got from living life forms and their turn for human use. Biological products are expected to continue to play a significant role in the future of medicine and health care. They include vaccines, serum, blood and blood products, gene therapy, antibodies, etc. The Indian administrative expert (CDSCO), is the body which is in charge of the advancement and promoting biologics in India. And in South Korea MFDS is responsible for regulations of biologics.

Objective: Unveiling the differences in regulatory approval aspects and documentation for biological products in India and South Korea as per CDSCO and MFDS respectively. Ensuring the safety, effectiveness, and quality of biological products requires various regulatory processes. These processes typically include rigorous testing, clinical Trails, quality control measure, and regulatory approvals by agencies like CDSCO in India and MFDS in South Korea. These steps are decisive to protect public health and ensure the biological products meet established standards before they made available to patients.

Keywords: Biological product; CDSCO; RCGM; GEAC; MFDS; KFDA; Comparative study; India; South Korea

1. Introduction

Biologicals are a diverse group of medicines which includes vaccines, growth factors, immune modulators, monoclonal antibodies, as well as products derived from human blood and plasma. ^[1] With speedy and advanced development of modern biological technology particularly recombinant DNA technology, biologic drug products have played more and more important roles in treating many life-threatening and chronic diseases. As a consequence, biologic drugs have comprised a growing segment in the pharmaceutical industry. ^[2] Biologics are not new ;development of human growth hormone, Insulin, Red blood cells, stimulating agents occurred decades ago, but the targets have increased exponentially with new genetic information and new understanding of sub cellular cascades and disease process. Scientific fields used in developing biologics include genomics and proteomics, as well as microarray, cell culture, and monoclonal antibody technologies^[3]

Due to the differences in their nature and how they are produced, biological therapeutics are regulated, tested, and controlled differently than other medicines. To help ensure their quality, safety, and efficacy, each batch of a biological therapeutic product must be tested extensively at each stage of production in order to ensure consistency with prior batches.^[1] In India, the regulations and registration framework for biologics and biosimilars falls under the purview of the Central Drugs Standard Control Organization (CDSCO), which operates under the Ministry of Health and Family

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Welfare.^[4] In South Korea, the regulation and registration of biologics and biosimilars falls under the oversight of the Ministry of Food and Drug Safety (MFDS), formerly known as the Korea Food and Drug Administration (KFDA).^[5]

The size of the Indian biosimilars market, which was predicted to be worth \$349 million in 2022, is expected to increase to \$2108 million in 2030 at a compound annual growth rate (CAGR) of 25.2%. The Indian government introduced the Biotechnology Industry Partnership Program (BIPP) in 2016 to help small and medium-sized biotech companies produce biosimilars.^[4] The Korean pharmaceutical market is estimated to be worth \$24.3 billion in 2019, and between 2015 and 2019, it grew at a compound annual growth rate (CAGR) of 5.0%. The export volume has been mounting with a CAGR of 15% with K-pharma actively establishing itself on the international market.^[5] The Department of Biotechnology in India is the office that controls the advancement, pre-clinical investigations of all Biologicals.^[6]

2. Overview of biologicals in India

Biological products, or biologics, are medical products. Many biologics are made from a variety of natural sources (human, animal or microorganism). Like drugs, some biologics are intended to treat diseases and medical conditions. Other biologics are used to prevent or diagnose diseases.

Examples of biological products include- vaccines blood and blood products for transfusion and/or manufacturing into other products, allergenic extracts, which are used for both diagnosis and treatment (for example, allergy shots) human cells and tissues used for transplantation (for example, tendons, ligaments and bone) gene therapies cellular therapies tests to screen probable blood donors for infectious agents such as HIV^[7]

The Indian administrative expert (CDSCO), is the body that is in charge of the improvement and upholding of biological products in India.^[8]

2.1. About CDSCO

The Central Drugs Standard Control Organization (CDSCO) is the Central Drug Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act. CDSCO has six zonal offices, four sub-zonal offices, 13 port offices and seven laboratories under its control.

Organization of CDSCO: Regulatory control over the import of drugs, approval of new drugs and clinical trials, meetings of Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB), approval of certain licenses as Central License Approving Authority is exercised by the CDSCO headquarters.

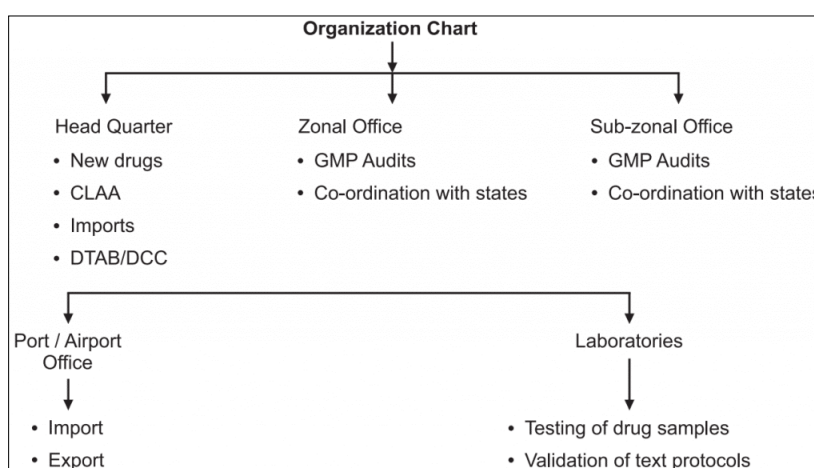


Figure 1 Organization of CDSCO

2.2. Functions of CDSCO

Drug Controller General of India is in authority for approval of licenses of specified categories of drugs such as blood and blood products, I.V. Fluids, Vaccine and Sera. Central Drugs Standard Control Organization Head quarter is located at FDA Bhawan, Kotla Road, New Delhi 110002 and functions under the Directorate General of Health Services.

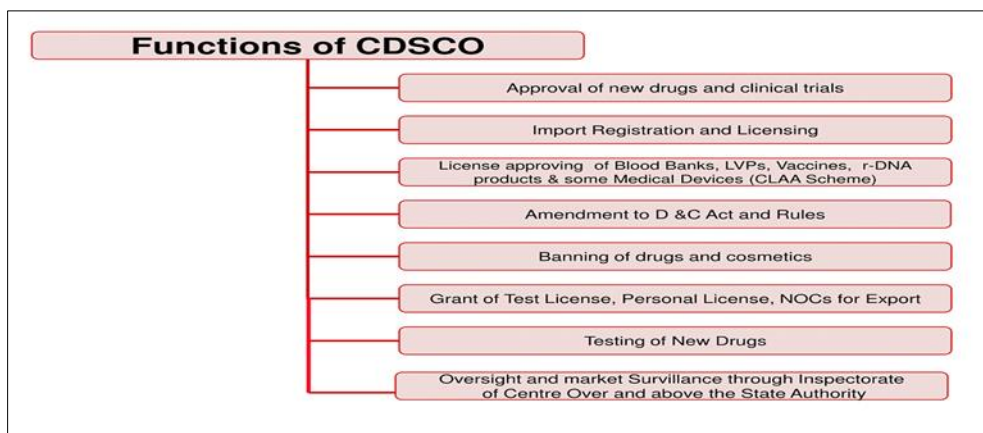


Figure 2 Functions Of CDSCO

3. Applicable guidelines and Regulations of Biologicals in India

The import and manufacture of drugs as well as biologicals are regulated under the provisions of drugs and cosmetic act 1940 and drugs and cosmetic rules 1945. The import and manufacture of biologicals without a license is an offence under the act.^[8]

Drug and Cosmetics Act 1945 and various rules for hazardous microorganisms/genetically engineered organisms or cells, 1989 regulate Similar Biologicals for the manufacture, use, import, export and storage. The list of various guidelines help in development of Similar Biologicals are shown in below.^[9]

- 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.^[5]

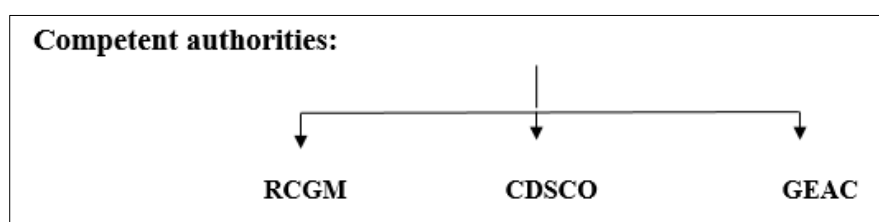


Figure 3 Important Authorities from which approval is needed for biological Products

3.1. Approval Process for Biologics

- **Clinical Trials:** The approval process for novel biologics involves conducting comprehensive preclinical and clinical trials to inaugurate their safety and efficacy.
- **Investigational New Drug (IND) Application:** Before conducting clinical trials, the manufacturer must submit an IND application to the regulatory authority. This application includes preclinical data, manufacturing information, and the proposed clinical trial protocol.
- **Clinical Trials:** Clinical trials for biologics follow a phased approach (Phase 1, Phase 2, and Phase 3), where safety, dosing, efficacy, and side effects are evaluated in increasing numbers of participants.
- **New Drug Application (NDA):** Once clinical trials are completed, the manufacturer submits an NDA containing comprehensive data on the biologic, including its manufacturing process, preclinical and clinical data, and information on safety and efficacy.
- **Review and Approval:** The regulatory authority assesses the NDA and associated data to conclude whether the biologic should be approved for marketing.^[4]

3.2. Preclinical and clinical Studies

3.2.1. Data requirements for pre-clinical studies

- The applicant should present the data created along with pre-clinical study protocols to RCGM for acquiring permission. Some of the information's are required such as: • Information on drug administration, dosage, absorption and eliminate rate • Mechanism of Action • Available toxicity data.
- **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. Ex: 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 accurate justification for sacrificing. 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
- **Immune response in animals:** The serum samples are experimented for reaction to host cell proteins. After the completion of pre-clinical studies, the reports are submitted to RCGM for review and deliberation.^[10]

3.2.2. Data requirements for clinical trial application

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

- **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 are : Half life , Linearity to pharmacokinetic parameters, Conditions and diseases to be treated Route of administration.
- **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.
- **Confirmatory safety and efficacy study:** This is mandatory for all the similar biologics in order to demonstrate its safety and efficacy. If trials are not vital it should be given elucidation 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
- **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. ^[10]

4. Data required for the application of market authorization

For marketing authorization, applicant must submit the application according to CDSCO norms and document for industry guidance 2008.

4.1. Post-Market data required for biologics

- **Pharmacovigilance plan:** It is the knowledge of pharmacology concerning to, detection, collection, consideration, monitoring and inhibition of adverse effects. 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.
- **Reporting of adverse reactions:** It is the reporting and analysing of all the adverse events occurred after the administration of product. Serious adverse events should be reported within 15 days as per schedule Y
- **Post Market Studies (PMS):** It is the practice of perceiving the safety of a pharmaceutical product after it has been released into the market. : The post-marketing studies are noted on the pharmacovigilance plan and updated studies should be submitted to CDSCO.
- **Information about the drug:** This includes identification, pharmacokinetic effects, adverse events and utilization.
- **Route of administration:** It is a pathway by which a drug is taken into the body. Common route of administrations is oral and intravenous.^[6]

5. Quality control of biologicals

Biologicals are complex molecules difficult to characterize and standardize given to inherent variability from batch to batch and their test/analysis requires highly keen facilities and domain expertise sustained by an animal facility. There are two laboratories at the national level, i.e. (1) central drugs laboratory, Kasauli, Himachal Pradesh; (2) National Institute of Biologicals, Noida, Uttar Pradesh, which are involved in quality control of biologicals. The central drugs 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 various biologicals.^[8]

5.1. Constricted Manufacturing Rules

The government of India confess the needs for constricted regulatory ideals. The Regulatory authorities declared tighter implementation to international good clinical practice (GCP) and WHO protocols. DCGI also uphold that it will initiate regular assessments 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 constricting the rules and enforcement, A new regulation "Schedule M" of the Drug and Cosmetics Act has now lay down the good manufacturing practices (GMP), requirements for factory premises and materials.^[6]

5.2. Overview of biologics in South Korea

Biologics are complex therapeutic substances produced using living organisms or their components, such as cells, proteins, nucleic acids, or tissues. They are used to prevent, treat, diagnose, or alleviate various medical conditions, including chronic diseases and rare disorders. Biologics can include monoclonal antibodies, vaccines, gene therapies, and other advanced therapeutic products.^[5]

In Korea, the high level regulation to license the drug or biological products is the same. All products are subject to the "Pharmaceutical Affairs Act". As a lower level regulation, there are KFDA notifications. Drugs and biological products including biotherapeutics comply with their own notification. "Notification of the regulation on review and authorization of biological products" are for biological products, and biosimilar products too.^[11]

5.3. Legal framework

In South Korea, the regulation and registration of biologics and biosimilars falls under the omission of the Ministry of Food and Drug Safety (MFDS), formerly known as the Korea Food and Drug Administration (KFDA).^[5]

South Korea utilizes a tiered, legal framework for enacting laws which includes acts, regulations, and guidance. The principal act through which the **Ministry of Food and Drug Safety** regulates cellular therapies is the **Pharmaceutical Affairs Act (PAA)**. Under the PAA cellular therapy products are classified as biologic products. The regulatory framework for biologic products is detailed in 7 regulations and 8 guidelines.^[12]

6. About MFDS

Ministry of Food and Drug Safety (MFDS) is a science-based regulatory agency responsible for the safety management of food, agricultural commodities, livestock and fishery products, drugs, biologics, herbal medicines, medical devices, quasi-drugs, cosmetics, and hygiene products to protect the public health. MFDS continues to expand its scope of product regulation by implementing new technologies to cultivate and establish strategies for regulatory science in Korea.^[13]

6.1. Organization of Ministry of Food and Drug Safety (Headquarters)

The MFDS consists of its headquarters, the National Institute of Food and Drug Safety Evaluation, and six regional offices (Regional Office of Food and Drug Safety).

6.2. Organization & Main Tasks

6.2.1. Biopharmaceuticals and Herbal Medicines Bureau

- **Biopharmaceutical Policy Division:** Generates & revises policies for biopharmaceuticals, transplantation materials and blood plasma and Supports exports and involves in international cooperation

- **Biopharmaceutical Quality Management Division:** Establishes & runs comprehensive domestic/international inspection plans concerning biopharmaceutical manufacturing, quality management criteria and human transplantation materials management.
- **Herbal Medicines Policy Division:** It grant market authorization of domestically-manufactured/imported products & develop relevant policies in herbal medicines
- **Cosmetics Policy Division:** Establishes and coordinate policies; implement & revise rules, regulations and notifications; make and coordinate monitoring plans in cosmetics products
- **Quasi-drugs Policy Division:** It grant market authorization of domestically-manufactured/imported products & develop relevant policies in quasi drugs
- **Biopharmaceuticals and Herbal Medicines Evaluation Department:**
- **Biologics Division:** Reviews & evaluates quality, safety and efficacy of biologics & biopharmaceutical diagnostics products and Approves domestic and import correlated products
- **Recombinant Products Division:** Reviews & evaluates quality, safety and efficacy of recombinants and Approves domestic and import related products
- **Cell and Gene Therapy Products Division:** Reviews & evaluates quality, safety and efficacy of cell therapies, gene therapies, tissue-engineered products and Approves domestic and import related products
- **Herbal Medicines Products Division:** Reviews & evaluates quality, safety and efficacy of herbal medicines and Approves domestic and import related products
- **Cosmetics Evaluation Division:** Reviews & evaluates quality, safety and efficacy of cosmetics and quasi medicines and Approves domestic and import related products^[13]

6.3. Biological approval process

The approval process for biological products in South Korea involves following steps:

- Investigational New Drug Application (IND) Review Process
- New Drug Application (NDA) Review Process
- **Authorization Process:** If the NDA approved ,the MFDS will issue an authorization for the biological product^[5]

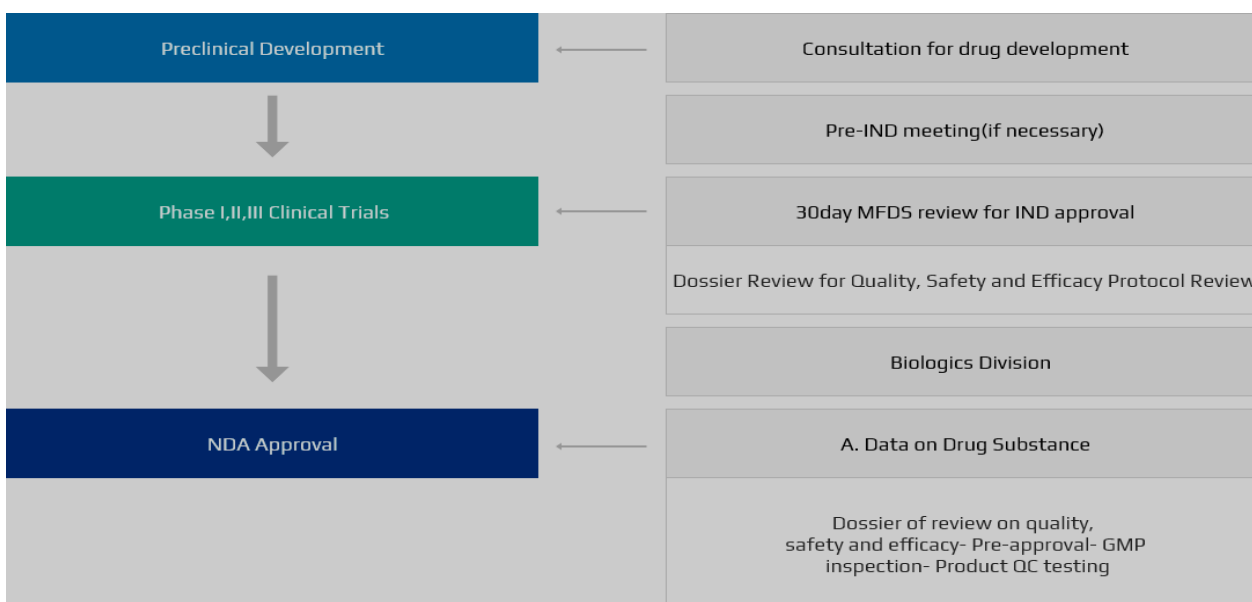


Figure 4 From development to authorization

6.4. IND (Investigational New Drug Application) Review Process

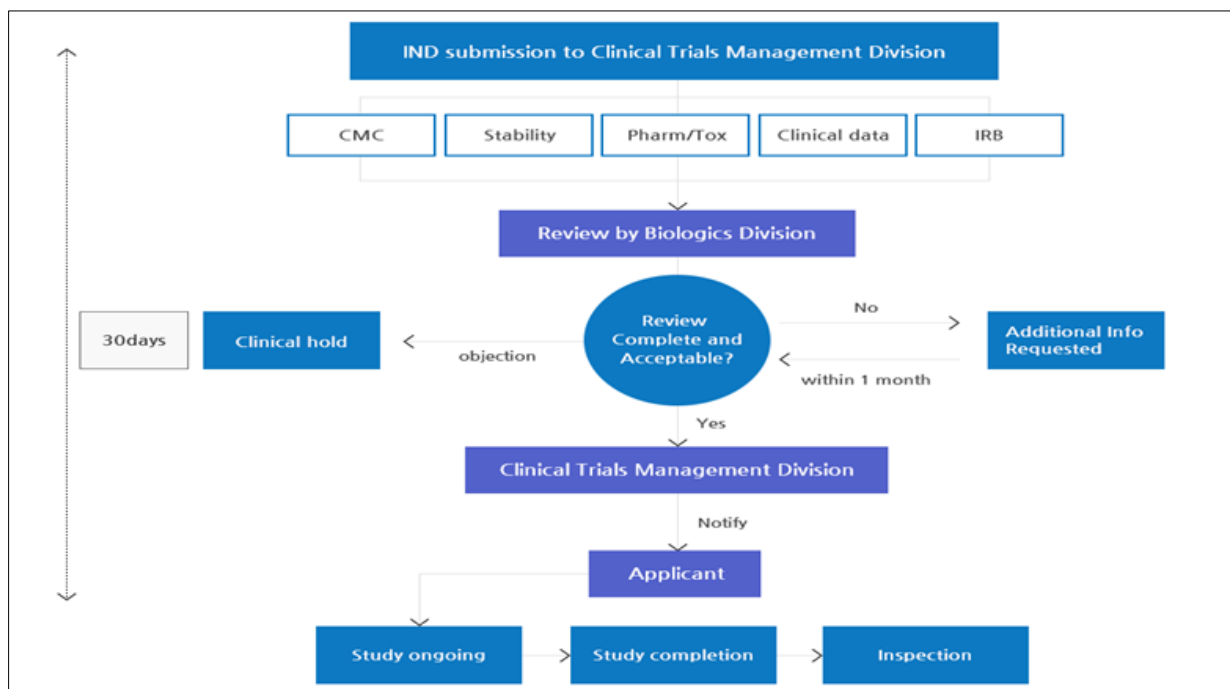


Figure 5 IND (Investigational New Drug Application) Review Process

6.4.1. Dossier for IND

- Development plan
- Introduction
- Data on structural identification and psychochemical and biological properties (including data for a placebo)
- Data on non-clinical studies: a) Data on Pharmacology b) Data on Toxicity
- Data on clinical studies (if applicable)
- Study protocol
- References
- Investigator’s Brochure (IB)

6.4.2. NDA (New Drug Application) Review Process

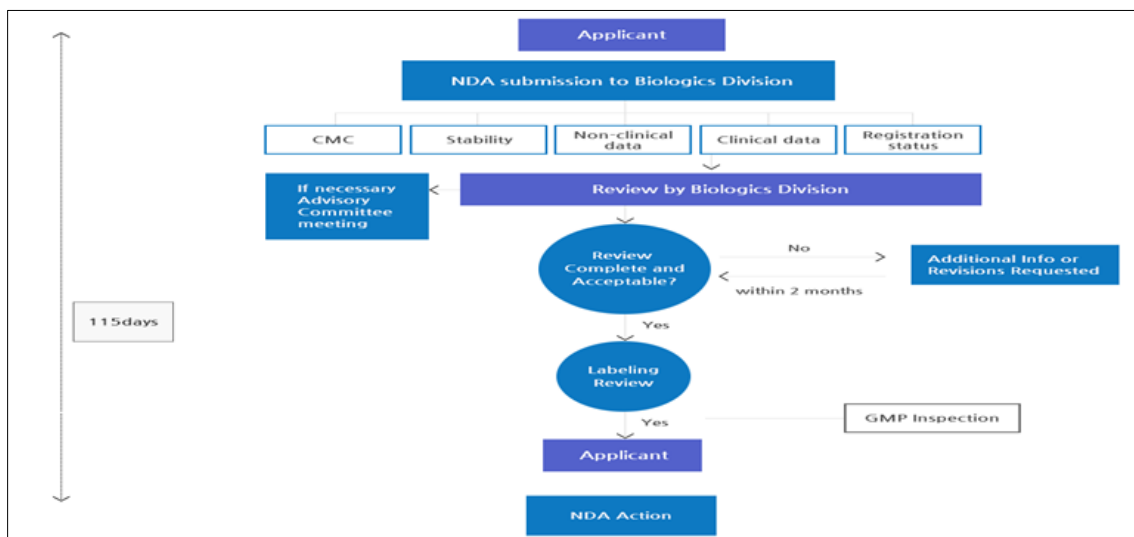


Figure 6 NDA (New Drug Application) Review process

6.5. Clinical Trial Requirements

- **Biologics (Innovative Products):** Clinical trials for innovative biologics in South Korea are more extensive and follow the traditional drug development pathway.
 - **Phase 1** trials focus on safety and dose-ranging, often comprising a small number of healthy volunteers.
 - **Phase 2** trials involve a larger number of patients to evaluate the drug's efficacy and optimal dosing.
 - **Phase 3** trials are larger, randomized, controlled trials that further evaluate efficacy and safety across diverse patient populations.
- Post-marketing studies (Phase 4 trials) may be required to monitor long-term safety and gather additional data.

6.6. Regulatory Process

- **Regulatory Submission:** Once clinical and analytical data are collected, a comprehensive regulatory submission is primed.
- **Regulatory Review:** The MFDS conducts a thorough review of the submitted data to assess the product's quality, safety, and efficacy.
- **Approval Decision:** Based on the review, the MFDS makes an approval decision. If the product meets the necessary standards, it receives regulatory approval for marketing and distribution. Timelines: The review period varies from 90 days to 120 days.

6.7. Post-marketing surveillance for biosimilars and biologics in South Korea

- **Reporting Adverse Events:** Healthcare professionals, patients, and other stakeholders are encouraged to report any adverse events, side effects, or unexpected reactions related to biologics and biosimilars to the MFDS. Manufacturers are also required to submit periodic safety update reports (PSURs) to the MFDS.
- **Pharmacovigilance System:** It includes continuous surveillance of adverse events, collection of safety data, and timely reporting to regulatory authorities.
- **Signal Detection:** It helps to identify any emerging safety issues that may not have been apparent during the pre-market clinical trials.
- **Risk Management Plans:** Manufacturers may be required to develop risk management plans to mitigate known and potential risks associated with their products.
- **Communication and Transparency:** Regulatory authorities maintain open communication with healthcare professionals, patients, and the public regarding safety information, regulatory actions, and updates related to biologics.
- **Collaboration with Global Regulatory Authorities:** Regulatory authorities often collaborate with other global regulatory agencies to share safety information and coordinate actions when needed.
- **Post-Market Studies:** In some cases, regulatory authorities may require manufacturers to conduct post-market studies to gather additional safety or efficacy data in real-world settings.
- Recall and Safety Alerts.^[5]

7. Comparative analysis of regulatory requirements for approval of biological products in India and South Korea

Table 1 Comparative analysis of regulatory requirements for approval of biological products in India and South Korea^[14]

Content	India	South korea
Regulatory Body	Central drug standard control organization CDSCO	Ministry of food and drug MFDS
Manufacturing:	Exploring India's Vast Range of Biologic Alternatives: Over 70 Products on the Market	Unveiling the Biosimilar Landscape in South Korea: 25 Manufacturers in Action
Key Eligibility Criteria for Applicants	Sponsor Companies, CROs, and Doctors Adhering to GCP Standards	Empowering Companies, CROs, and Doctors to Secure IND Holder Designation
Flow of clinical trial notification	Initiated after approval from CDSCO	There is no clinical trial notification. Only IND approval is available .

Comparative Analysis of Language Usage in Application Materials	Submit All Application Materials in English	Korean in the Module 2, respectively
Approval review organization	CDSCO AND DCGI (drug control general of India)	MFDS And NiFDS (National institute of food and drug safety Evaluation)
Approval review time	12 -15 months for marketing approval and registration certificate	10- 15 months
Manufacturing and Marketing permission	CDSCO	MFDS
Example for top biological products manufacturing companies	Titan biotech Ltd. Biocon Lupin Limited Merck and Co Reddy's Laboratories	Samsung Biologics Co, Celltrion inc. CKD Bio Corp LG Chem Ltd
Packaging Labels and required contents for packaging	Should be written in English Requirements: contents described in rule 96 and schedule D2 of D and C rules 1945	In Korean Language Requirements: Article 56 of the Pharmaceutical Affairs Act, Article 75 of the Enforcement regulation of Pharmaceutical Affairs Act
Evaluation of GMP system for manufacturing and post approval	Original GMP in India	Under application to PIC
Required number of local subjects for clinical trials	Over 100 subjects in Phase 3	In Korea, Significant number needs to show similarity in response.

8. Conclusion

In conclusion, CDSCO and MFDS have similar goals and functions, but have differences in their approval processes. Both regulatory bodies require submission of preclinical and clinical data, as well as data on manufacturing and quality control. The main difference is the time taken for approval. Navigating regulatory pathways can be challenging, but with a thorough understanding of the requirements and close collaboration with the regulatory bodies, approval can be obtained.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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