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# Regulatory Requirements for Marketing Authorization of Different Categories of Drugs in India

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**ABSTRACT**

India is a pool of diverse population base of more than 1.2 billion and is a home for a numerous diseases, Institutions and hub of contract manufacturers and researchers, and India has the second largest number of FDA-approved plants for ingredients and formulations. India is today one of the top emerging markets in the global pharmaceutical market. The sector is highly knowledge based and its steady growth is positively affecting the Indian economy. The organized nature of the Indian pharmaceutical industry is attracting several companies that are finding it viable to increase their operations in the country. Further, India is home to about 10,500 manufacturing units and over 3,000 pharma companies. India exports all forms of pharmaceuticals from APIs to formulations, both in modern medicine and traditional Indian medicines.

## INTRODUCTION:

### Indian Pharmaceutical Industry:

Geographically, India is comprised area of 3.29 million sq. km. (1.27 million sq. mi.); about one-third the size of the USA. Genetically, culturally and socio-economically diverse population base of more than 1.2 billion is a home for numerous diseases as well as for qualified, English-speaking professionals, Institutions and hub of contract manufacturers and researchers [1, 2]. Today, Indian economy stand as the third largest based on the Purchasing Power Parity (PPP) and in terms of globally eleventh largest by nominal Gross Domestic Product (GDP), due to its rapid growth, especially over the last decade, India is considered an industrialized nation[3]. Apart from being a multi-ethnic, pluralistic society, India is also blessed with a variety of wildlife.

McKinsey & Company a global management and consulting firm, through a major study it has reported that by 2020 India's pharmaceutical sector will touch US$ 45 billion. The reasons for this optimism are well founded. In the period 2002–2012, the country's healthcare sector grew three times in size, touching US$ 70 billion from US$ 23 billion. India's pharmaceutical market experienced a similar boom, reaching US$ 18 billion in 2012 from US$6 billion in 2005. The report further states that the Indian pharmaceutical market will be the sixth largest in the world by 2020. The rise of pharmaceutical outsourcing and investments by multinational companies (MNCs), allied with the country's growing economy, committed health insurance segment and improved healthcare facilities, is expected to drive the market's growth. India is today one of the top emerging markets in the global pharmaceutical scene.

The sector is highly knowledge based and its steady growth is positively affecting the Indian economy. The organized nature of the Indian pharmaceutical industry is attracting several companies that are finding it viable to increase their operations in the country. Further, India is home to about 10,500 manufacturing units and over 3,000 pharma companies. India exports all forms of pharmaceuticals from APIs to formulations, both in modern medicine and traditional Indian medicines[4].

Biosimilars development pose different challenges when compare to small molecule generics, with additional requirements in terms of:

• Sophisticated technologies

• Clinical development, clinical trial expertise and proving comparative data

• Market access

• Manufacturing in dedicated manufacturing facility

• Sales and marketing capabilities[5]

**METHODOLOGY:**

**Description of Biologic and Biosimilars:**

**Biologic:**

A biologic medicine is a large molecule typically derived from living cells and used in the treatment, diagnosis or prevention of disease. These are produced by using biotechnology procedures like r-DNA technology. Biologic medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies and fusion proteins. Biologics are distinct from small molecule drugs in that they are larger, and are far more structurally complex agents. Biologic medicines are often 200 to 1,000 times the size of a small molecule drug. They are also highly sensitive, making them more difficult to characterize and produce. Due to both their size and sensitivity, biologic medicines are almost always injected into a patient's body[6].

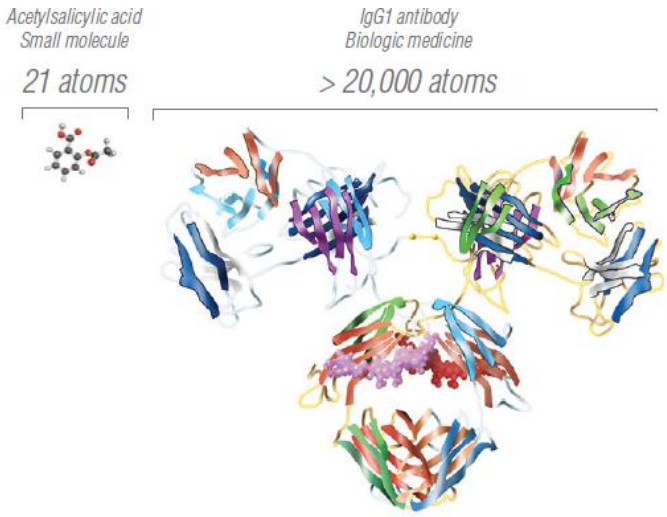



**Figure 1: Structural difference between chemical entity drugs and biologic medicines**

**Reference innovator product for biosimilars:**

- Reference innovator product must have same active substance as of the proposed similar biologic.

- The dosage, form and route of administration of the similar biologic should be same as that of reference innovator product.
- Reference innovator product should have been authorized for approval in India to confirm its quality, safety and efficacy. In cases where reference innovator product is not authorized in India, it should have been approved in countries with well established regulatory systems such as US FDA, EMA etc. and should have been in use for at least four years.
- Another similar biologic cannot be considered as reference innovator product, as the reference innovator product should be the one that has been licensed based on a full quality, safety and efficacy data.
- Same reference innovator product should be used throughout the development of a similar biologic i.e. manufacturing process, comparability exercise, pre-clinical and clinical evaluation.
- The acceptance of a reference innovator product for evaluation of a similar biologic does not imply approval for use of the reference innovator product in India.
- In case the reference biologic is not marketed in India, the reference biologic should have been licensed and widely marketed for 4 years post approval in innovator jurisdiction in a country with well established regulatory framework. In case no medicine or only palliative therapy is available or in national healthcare emergency, this period of 4 years may be reduced or waived off[7,8].

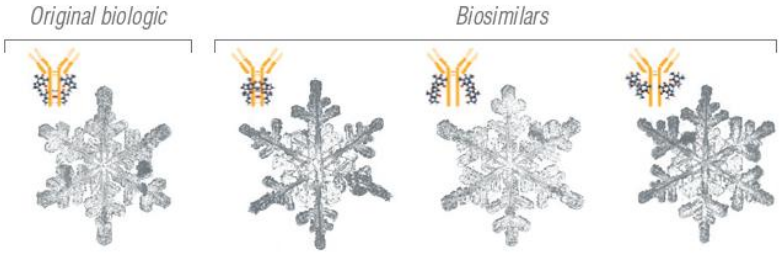



**Figure 2: Original biologic and Biosimilars**

**Biosimilars (similar biologics):**

**Table 1: Comparative table for definition of biosimilars across global**

| INDIA | UNITED STATES | EUROPE |
|---|---|---|
| As per the Indian Biosimilars guidelines, similar biologic includes: a biological product or drug produced by genetic engineering techniques and claimed to be "similar" in terms of quality, safety, efficacy to a reference innovator product, which has been granted a marketing authorization in India by DCGI on the basis of the regulatory regime (complete dossier) and with a history of safe use in India[7]. | A biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product [6]. | A biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). When approved, a Biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness[6]. |

**Table 2: Different terminology used for the word biosimilars across Global**

| COUNTRY/AUTHORITY | TERM |
|---|---|
| WHO | Similar biotherapeutic products |
| USFDA, Japan | Follow-on protein products/Follow-on biologics |
| Canada | Subsequent entry biologics |
| EMA, Korea, India, China, Australia | Biosimilars |

**COMPARISON BETWEEN BIOSIMILARS AND BIOLOGICS:**

A biosimilar medicine is analogous to a biological medicine that has already been approved (the 'biologic reference medicine') and they are the genetic versions of biologics. The active ingredient of a biosimilar medicine is analogous to the biological reference medicine. Biosimilar and biological reference medicines are given in general at the same dose to treat the same disease.

Based on these different definitions, there are three determinants in the definition of the biosimilar product:

i. It should be a biologic product;

ii. The reference product should be a previously licensed biologic product;

iii. The demonstration of high similarity in safety, quality, and efficacy is obligatory[9].

**Table 3: Differences between Generic, Biologics and Biosimilars**

| GENERIC | BIOLOGICS | BIOSIMILARS |
|---|---|---|
| Chemical and therapeutic equivalent of original low molecular weight drug whose patent has expired. | Biological medicinal products developed through biopharmaceutical techniques such as:<br>• Recombinant DNA technology<br>• Cell fusion | Biological product referring, but not identical to an existing product, submitted for separate marketing approval following patent expiration. |

Similar biologics are not expected to be direct copies of biologic medicines and are therefore not the same as generic drugs. Due to the complex structure of biologic medicines and the processes involved in production, biosimilars must be shown on the basis of analytical, non-clinical and clinical data to be similar to an original biologic in terms of structural characteristics, and safety and efficacy. Minor differences with the active ingredient are expected and permitted so long as any such differences are demonstrated not to be clinically meaningful[6].

**Table 4: Comparison of Generics and Biosimilars**

| | GENERICS | BIOSIMILARS |
|---|---|---|
| Definition | A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. A generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. | A biological product or drug produced by genetic engineering techniques and claimed to be "similar" in terms of quality, safety, efficacy to a reference innovator product. |
| Product related differences | • Produced by chemical synthesis<br>• these are far smaller (<500 Da), i.e., mol.wt,1000, self-contained, organic molecules | • Biotechnologically produced by host cell lines<br>• 100 to 1000 times larger in size (5000-3,00,000 Da), having several hundred amino acids (average |

| | | |
|---|---|---|
| | • Well-defined physiochemical properties<br>• Usually Stable<br>• Single entity, high chemical purity, purity standards well established<br>• Identical copy can be made<br>• Administered through different routes of administration.<br>• Rapidly enters systemic circulation through blood capillaries.<br>• Distribution to any combination of organ/tissue<br>• Often specific toxicity<br>• Often non-antigenic | molecular weight of 150 per amino acid), biochemically joined together in a defined sequence by peptide bonds to form a polypeptide.<br>• Complex physiochemical properties<br>• Often unstable, Sensitive to heat and shear (aggregation), may require specific formulation<br>• Heterogeneous nature, broad specifications which may change during development, difficult to standardize<br>• Impossible to ensure identical copy.<br>• Usually administered parenterally<br>• Larger molecule primarily reach circulation via lymphatic system, subject to proteolysis during interstitial and lymphatic transit<br>• Distribution usually limited to plasma and/or extracellular fluid<br>• Mostly receptor mediated toxicity<br>• Usually antigenic |
| Manufacturing differences | • Completely characterized by analytical methods<br>• Easy to purify, costs cheap<br>• Contamination can be generally avoided, easily detectable and removable<br>• Not affected by slight changes in production process and environment<br>• Reproducibility easy to establish | • Difficult to characterize<br>• Lengthy and complex purification process & isolation, expensive<br>• High possibility of contamination, detection is harder and removal is often impossible<br>• Highly susceptible to slight changes in production process and environment<br>• Reproducibility difficult to establish |
| Clinical development | • Limited clinical activities, often only phase 1 PK/PD studies<br>• Short timeline for approval<br>• Development costs up to 5 m$<br>• Enrolment of around 20-100 subjects | • Extensive clinical trial activities, including phase 1 & 3 studies.<br>• Pharmacovigilance and periodic safety updates after launch needed<br>• Development costs around 350-800m$ |

| | | |
|---|---|---|
| | | • Timeline of 6-15 years<br>• Enrolment of >1000 patients/subjects |
| Marketing | • Large price discounts<br>• No or limited detailing to physicians<br>• Key role of wholesalers and payers<br>• Special delivery device not usually necessary<br>• Automatic substitution is possible in some pharmacies<br>• Simple to distribute | • Smaller price discounts; price sensitivity is product-specific<br>• Detailing to specialist physicians required<br>• Method of delivery can be a key differentiator<br>• No automatic substitution<br>• Specialist distribution often required |
| Regulation | • Must be identical to reference product<br>• Substitutable/interchangeable<br>• Abbreviated procedure is applicable to all drugs | • Must be highly similar to reference product<br>• Not automatically substitutable<br>• Abbreviated approval requirements vary depending on the drug |

**Table 5: Comparision in Development Stages of Generics, Biosimilars and Originators**

| **Activities** | **Generics** | **Biosimilars** | **Reference biologics(originators)** |
|---|---|---|---|
| No. of patients in various phases of development | 20-50 patients | ~500 patients | ~1000-2000 patients |
| Time to market | 2-3 years | 7-8 years | 8-12 years |
| Development costs | USD 2 million-3 million | USD 100 million-150 million | USD 500 million-1 billion |
| Success probability | 90-99% | 50% | 5% |

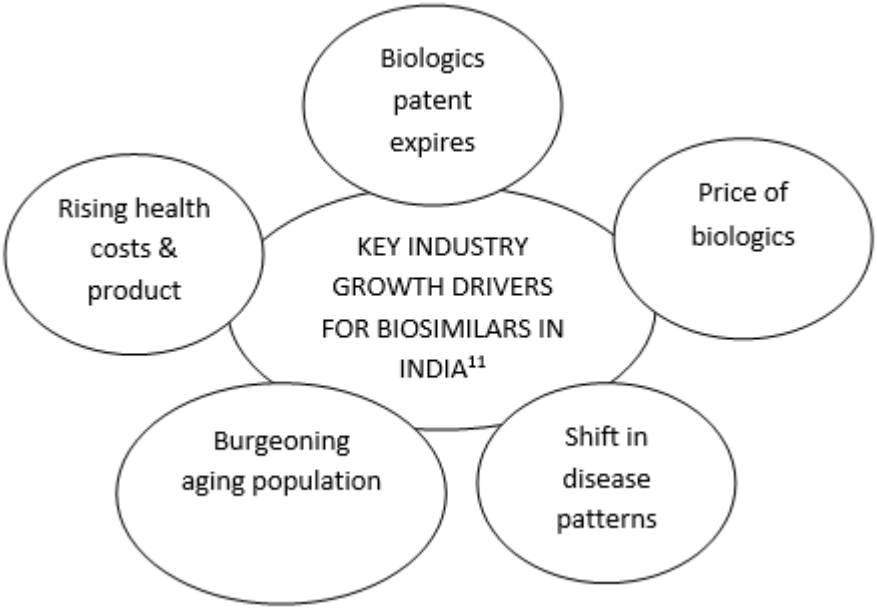



**Figure 3: Industry Growth Drivers**


**Figure 4: Flow Chart of Strategy Followed for Methodology**

**Table 6: Application Forms and corresponding licenses for Indian Regulatory Authorities to carry out development stage of products**

| Application types | Application Form No. | License Form No. | Regulatory body | Validity | Timelines in Days |
|---|---|---|---|---|---|
| Import of drugs for the purpose of examination, test or analysis | Form 12 | Form 11 | CDSCO | 1 Year | 45 |
| NOC for manufacture for the purpose of examination, test or analysis (Form 29) | - | NOC | CDSCO | - | 60# |
| Manufacture for the purpose of examination, test or analysis | Form 30 | Form 29 | SLA | 1 Year | |

**Table 7: The list of various applications to CDSCO/ state licensing authorities (SLA) for drug import, site registration, manufacture and marketing authorization**

| Application types | Application Form No. | License Form No. | Regulatory body | Validity | Timelines in Days |
|---|---|---|---|---|---|
| Import of a new drug (DP)/ (DS) | Form 44 | Form 45/ Form 45 A | CDSCO | - | 180 |
| Manufacture of New Drug (DP)/ (DS) | Form 44 | Form 46/ Form 46 A | CDSCO | - | 180 |
| Permission to undertake clinical trial | Form 44 | NOC | CDSCO | | 180 |
| Registration certificate for import of Drugs into India | Form 40 | Form 41 | CDSCO | 3 Years | 270 |
| Import license for drugs for commercial use | Form 8 | Form 10 | CDSCO | 3 Years | 45 |
| Manufacture for sale or distribution (Mfr.) | Form 24 | Form 25 (Fresh) Form 26 (Renewal) | SLA | 5 Years | 30 |

| | | | | | |
|---|---|---|---|---|---|
| Mfr. of Drugs specified in schedule C & C (1) and not in schedule X | Form 27 | Form 28 (Fresh) Form 26 (Renewal) | | 5 Years | 30 |
| Mfr. of LVP/Sera and Vaccines excluding those specified in Schedule X | Form 27 D | Form 28 D | | 5 Years | 60 |
| Mfr. of Loan licenses except schedule C & C (1) and X | Form 24 A | Form 25A (Fresh) Form 26A (Renewal) | Concerned SLA | 5 Years | 30* |
| Sale license to sell, stock or exhibit or offer for sale or distribution of drugs(Drugs other than and X) | Form 19 | Form 20 (Retail) Form 20 B (Wholesale) | | 5 Years | 30* |
| Sale license drugs specified in schedule X and not in schedule C & C (1) | Form 19 C | Form 20F (Retail) Form 20 G (Wholesale) | | 5 Years | 30* |
| #If inspection of premises involved, the timelines will be considered from the date of receipt of the inspection report<br>*Timelines vary state to state licensing authority | | | | | |

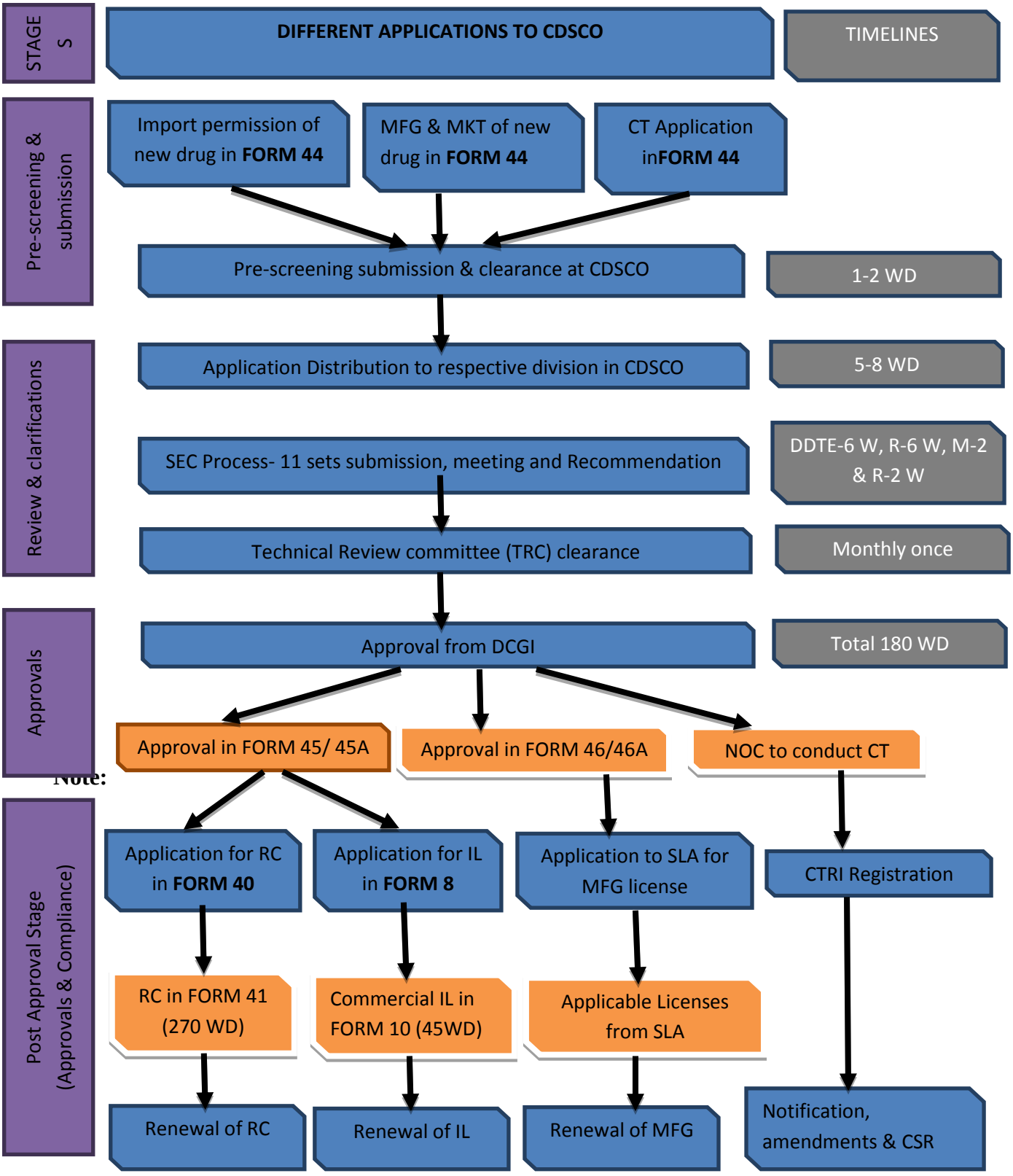
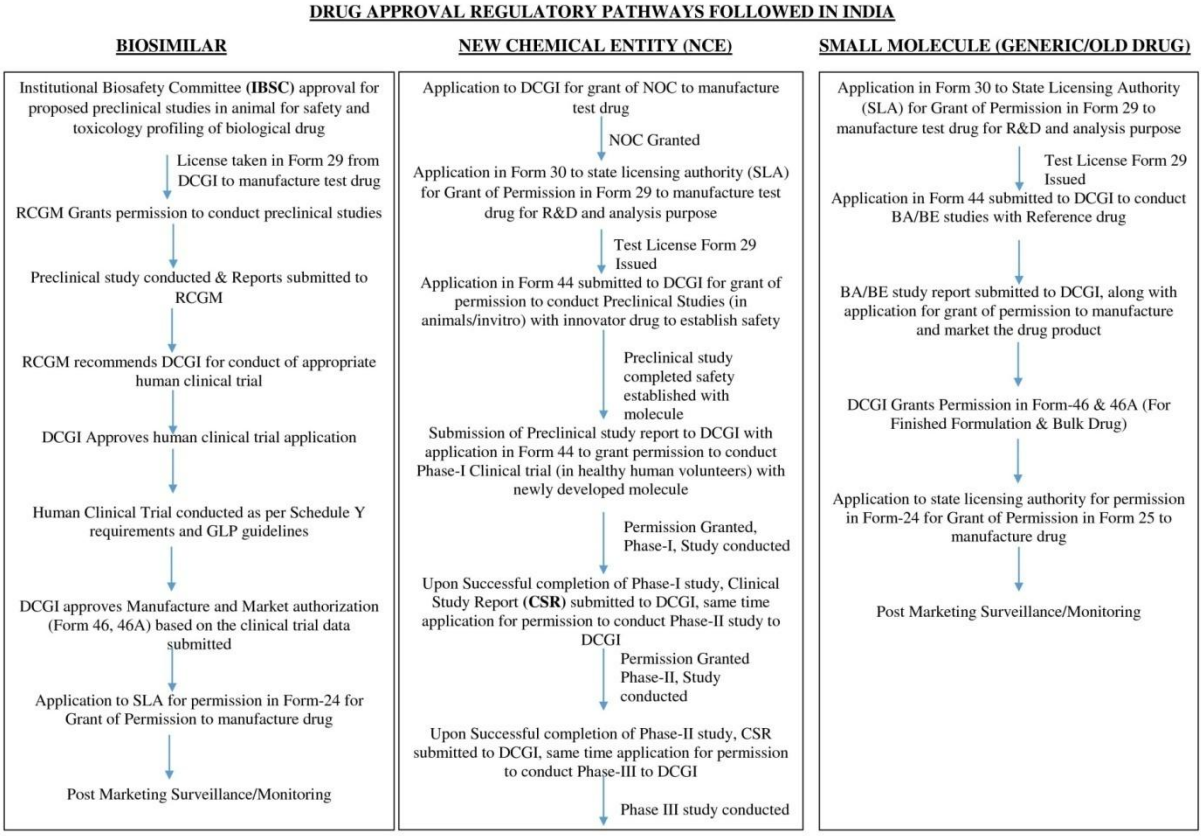
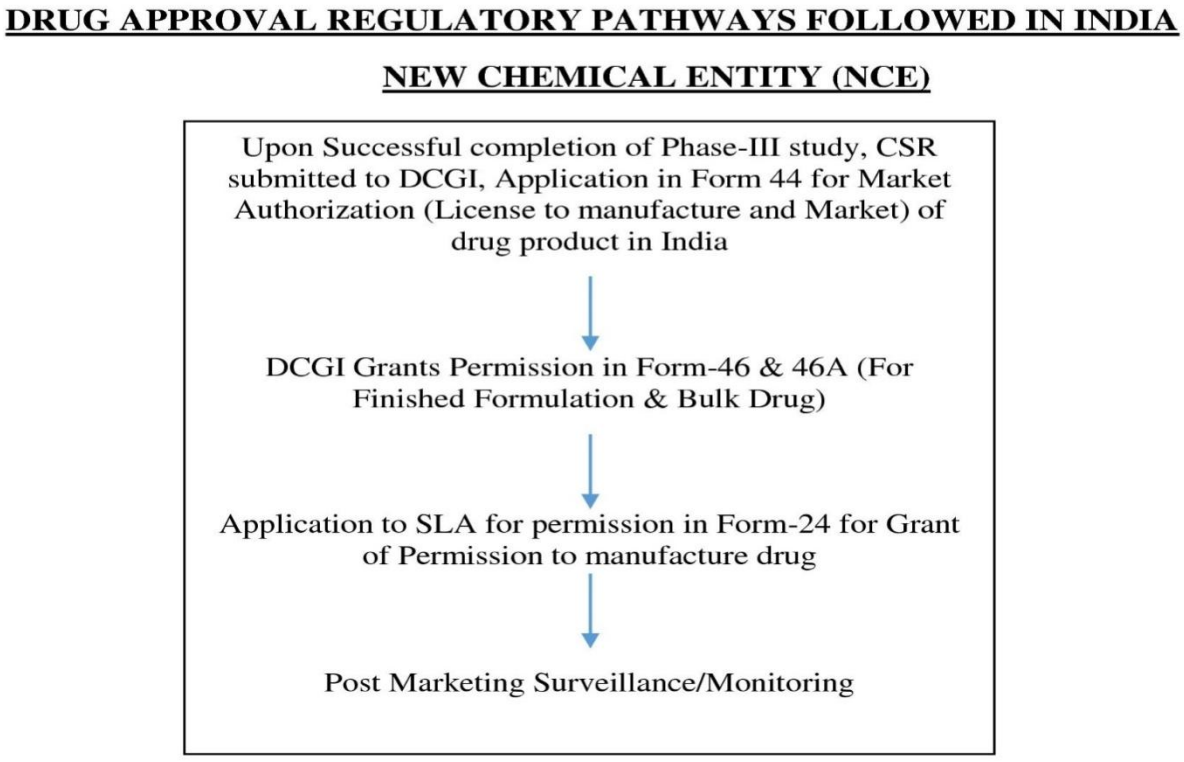



**Figure 5: REGULATORY PATHWAY FOR NEW DRUGS (CT, MAA, RC and Import) APPLICATIONS AT CDSCO**


DRUG APPROVAL REGULATORY PATHWAYS FOLLOWED IN INDIA
BIOSIMILAR
Institutional Biosafety Committee (IBSC) approval for proposed preclinical studies in animal for safety and toxicology profiling of biological drug
License taken in Form 29 from DCGI to manufacture test drug
RCGM Grants permission to conduct preclinical studies
Preclinical study conducted & Reports submitted to RCGM
RCGM recommends DCGI for conduct of appropriate human clinical trial
DCGI Approves human clinical trial application
Human Clinical Trial conducted as per Schedule Y requirements and GLP guidelines
DCGI approves Manufacture and Market authorization (Form 46, 46A) based on the clinical trial data submitted
Application to SLA for permission in Form-24 for Grant of Permission to manufacture drug
Post Marketing Surveillance/Monitoring
NEW CHEMICAL ENTITY (NCE)
Application to DCGI for grant of NOC to manufacture test drug
NOC Granted
Application in Form 30 to state licensing authority (SLA) for Grant of Permission in Form 29 to manufacture test drug for R&D and analysis purpose
Test License Form 29 Issued
Application in Form 44 submitted to DCGI for grant of permission to conduct Preclinical Studies (in animals/invitro) with innovator drug to establish safety
Preclinical study completed safety established with molecule
Submission of Preclinical study report to DCGI with application in Form 44 to grant permission to conduct Phase-I Clinical trial (in healthy human volunteers) with newly developed molecule
Permission Granted, Phase-I, Study conducted
Upon Successful completion of Phase-I study, Clinical Study Report (CSR) submitted to DCGI, same time application for permission to conduct Phase-II study to DCGI
Permission Granted Phase-II, Study conducted
Upon Successful completion of Phase-II study, CSR submitted to DCGI, same time application for permission to conduct Phase-III to DCGI
Phase III study conducted
SMALL MOLECULE (GENERIC/OLD DRUG)
Application in Form 30 to State Licensing Authority (SLA) for Grant of Permission in Form 29 to manufacture test drug for R&D and analysis purpose
Test License Form 29 Issued
Application in Form 44 submitted to DCGI to conduct BA/BE studies with Reference drug
BA/BE study report submitted to DCGI, along with application for grant of permission to manufacture and market the drug product
DCGI Grants Permission in Form-46 & 46A (For Finished Formulation & Bulk Drug)
Application to state licensing authority for permission in Form-24 for Grant of Permission in Form 25 to manufacture drug
Post Marketing Surveillance/Monitoring


DRUG APPROVAL REGULATORY PATHWAYS FOLLOWED IN INDIA
NEW CHEMICAL ENTITY (NCE)
Upon Successful completion of Phase-III study, CSR submitted to DCGI, Application in Form 44 for Market Authorization (License to manufacture and Market) of drug product in India
DCGI Grants Permission in Form-46 & 46A (For Finished Formulation & Bulk Drug)
Application to SLA for permission in Form-24 for Grant of Permission to manufacture drug
Post Marketing Surveillance/Monitoring

**Stepwise Procedures for the Development of r-DNA Biosimilars Products**

**Constitution of Institutional Biosafety committee (IBSC):**

Application to DBT for creation of IBSC

↓

DBT approves & appoints a Govt. nominee in ISC

↓

Formation of IBSC

↓

IBSC meetings

Ref: Guidelines & Handbook for IBSC; 2nd revised version May 2011

New product development

↓

Submit application in Form B1 to RCGM

**Requirements for import license:**
1. Applicant name
2. Description of GMO
3. Quantity of GMO
4. Source of GMO
5. Objective of the proposal
6. Mode of shipment
7. Information on containment facilities installed at R& D & production premises (whichever is applicable)
8. SOP on decontamination, disposable mechanisms & risk management

Copies: 23

↓

Clearance in Form B2 from RCGM

↓

Submit application Form 12 with RCGM

Recommendation to DCGI

**Requirements for import license:**
1. Form 12 (application) clearly indicate the name of country, manufacturer, generic name, composition of drug & therapeutic class
2. Mfg-form 29: Purpose of import and detailed utilization indicating nature of tests and quantity required for test
3. An undertaking that drugs imported under test license would be used for test & analysis
4. Detailed information regarding import of same drug during last 3 years along with certificate destruction of unused drug

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Form 11 from DCGI (License to import drugs/strains/kit for the purposes of examination, test or analysis

**Development phase**

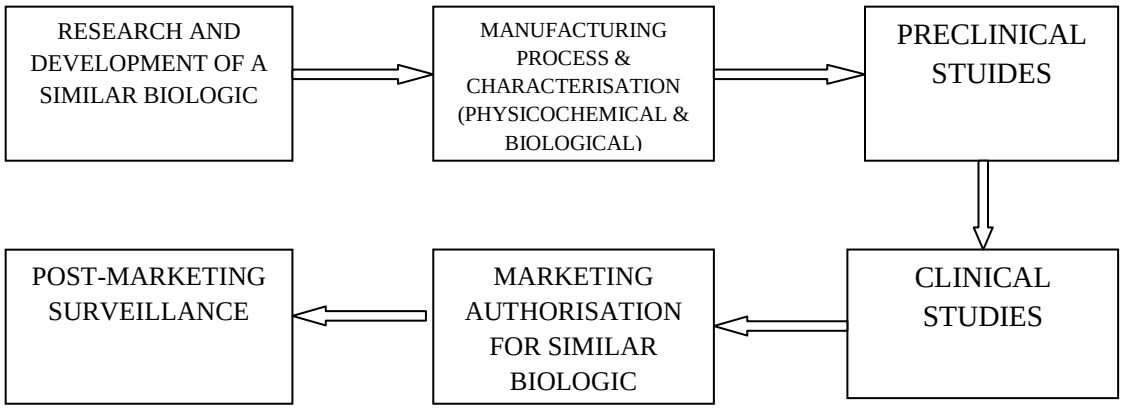


**Figure 6: Steps involved in the Development and Marketing of a Biosimilar**

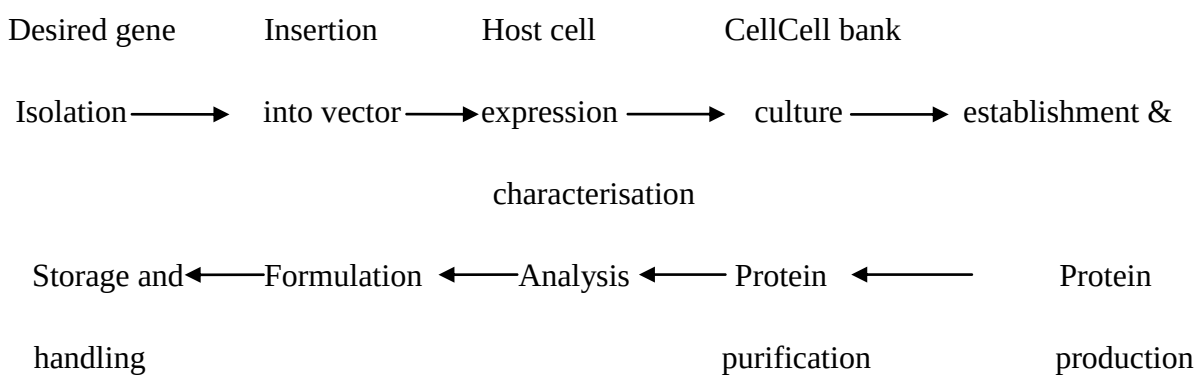


**Figure 7: Typical steps in the Manufacture of a biological product**

**CONCLUSION:**

In the present scenario, India has stringent regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application (MAA) of a new drug product belonging to various categories of drugs (NCE, Biologicals, Controlled Drugs etc.) is utmost difficult. Therefore, the knowledge of precise and detailed regulatory requirements for MAA of different categories of drugs should be known to establish a suitable regulatory strategy. The drug approval process from regulatory authorities for different categories of pharmaceutical products and also provides a perspective on the development of Indian pharmaceuticals regulatory process from pre-independence era to till date.

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