Role of Regulatory Authorities in Marketing Regulation of Drugs in India

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Abstract
Approval of the drug product for import, manufacturing and marketing in India, its demonstration for safety and efficacy in humans is essential. The Rules 122A, 122B and 122D, 122 DA, 122DAA, 122E and Appendix I, IA and VI of Schedule Y of the Drugs & Cosmetics Act, 1945, describes the information/data required for approval of clinical trial and/or to import, manufacture, or market any new drug in the country. However, the requirements for approval of clinical trials and new drugs may vary depending on the nature of new drugs.

1.0 Introduction[1-4]

Government oversight of the pharmaceutical industry is usually classified into preapproval and post-approval categories. Most of the therapeutically significant compounds marketed today are the subject of new drug applications (NDAs) and abbreviated new drug applications (ANDAs). Preapproval activities, based on these detailed applications, are used to assure the drug is safe and effective before marketing. After the drug is approved and marketed, periodic unannounced inspections of drug production and control facilities by FDA's field investigators and analysts are conducted. The FDA uses different mechanisms for assuring that firms adhere to the terms and conditions of approval described in the application and that the drug is manufactured in a consistent and controlled manner. The Federal Food drug and Cosmetic Act (FD&C Act) provides legal authority for inspection. These regulations, Current Good Manufacturing Practice for Finished Pharmaceuticals, are contained in Part 211 of Title 21 of the U.S. Code of Federal Regulations. This regulation contains requirements for Organization and Personnel; Buildings and Facilities; Equipment; Components, Containers, and Closures; Production and Process Control; Packaging and Labeling; Distribution; Laboratory; and Reports and Records. The regulations are general enough to be applied to a wide variety of dosage form drugs from topical ointments and creams to sterile injectables and ophthalmics. FDA investigators often use additional information from a variety of market surveillance systems to assist them in identifying a manufacturing or control problem. These laboratories confirm suspected chemical, physical, and microbiological problems with pharmaceuticals; verify and develop analytical methods; and conduct research. This system of regulation has grown with the pharmaceutical industry through many crises and challenges. The FDA welcomes dialogue with other regulatory bodies, industry organizations, Congress, and the public to improve the efficiency of its regulatory and administrative processes.

2.0 Regulatory Process[5]

To enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs, every country has its own regulatory authority. Thus a regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, which is also known as drug approval process is necessary. In general, various stages for the approval of the drugs comprises: application to conduct clinical trials, application to marketing authorization of drug and post-marketing studies.

3.0 Regulatory Framework- Drugs Sector[6-8]

The manufacture, sale, import, exports and clinical research of drugs and cosmetics under the current Indian legal and regulatory regime is governed by the following laws:-

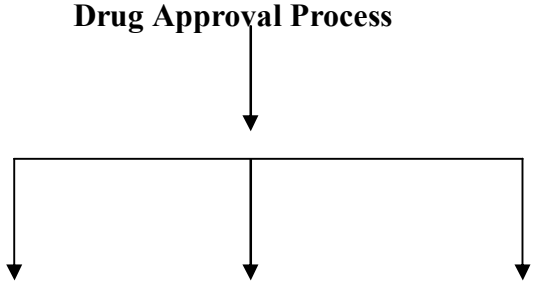
1. The Drugs and Cosmetics Act, 1940
2. The Pharmacy Act, 1948
3. The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954
4. The Narcotic Drugs and Psychotropic Substances Act, 1985
5. The Medicinal and Toilet Preparations (Excise Duties) Act, 1956
6. The Drugs (Prices Control) Order 1995 (under the Essential Commodities Act.
7. The Industries (Development and Regulation) Act, 1951
8. The Trade and Merchandise Marks Act, 1958
9. The Indian Patent and Design Act, 1970
10. The Factories Act.

4.0 The Current Regulatory System[9-10]

1) **The Central Drug Standards and Control Organization (CDSCO) -** Located under the aegis of the Ministry of Health and Family Welfare. The standards and measures for ensuring the safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in the country; are prescribed by CDSCO. It also regulates and supervises the market authorization for new drugs, clinical trials standards, drugs imports and approves licenses to manufacture the products.
2) **Drug Regulatory Authorities (DRAs)** - The DRAs have been susceptible to influence by local political authorities, and in some cases have been able to do little to prevent illegal drug manufacturing and marketing activities. However sometimes the staffing problems, combined with their relatively limited technical experience in regulatory issues, land themselves into a difficult situation yet manufacturers that set up operation in states where regulatory oversight and enforcement are weakest can then market their drugs in the rest of the country.

5.0 Drug Approval Process in India[11]

Drug approval process in India comprises of three main registration processes, which are New Drug Application (NDA), Abbreviated New Drug Application (ANDA), and Investigational New Drug Application (IND), which are depicted in flow chart below:



NDA ANDA IND

5.1 NDA (New Drug Application) [12-13]

For decades, the regulation and control of new drugs has been based on the New Drug Application (NDA). The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization.

5.2 NDA Classification

CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses.

1. New Molecular Entity
2. New Salt of Previously Approved Drug (not a new molecular entity)
3. New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
4. New Combination of Two or More Drugs
5. Already Marketed Drug Product - Duplication (i.e., new manufacturer)
6. New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription to OTC)
7. Already Marketed Drug Product - No Previously Approved NDA

5.3 Fundamentals of NDA Submissions

Although the quantity of information and data submitted in NDAs can vary significantly, the components of NDAs are more uniform. The components of NDA for Human Use consist of as many as 15 different sections:

- Index;
- Summary;
- Chemistry, Manufacturing, and Control;
- Samples, Methods Validation Package, and Labeling;
- Nonclinical Pharmacology and Toxicology;
- Human Pharmacokinetics and Bioavailability;

- Microbiology (for anti-microbial drugs only);
- Clinical Data;
- Safety Update Report (typically submitted 120 days after the NDA's submission);
- Statistical;
- Case Report Tabulations;
- Case Report Forms;
- Patent Information;
- Patent Certification; and
- Other Information.

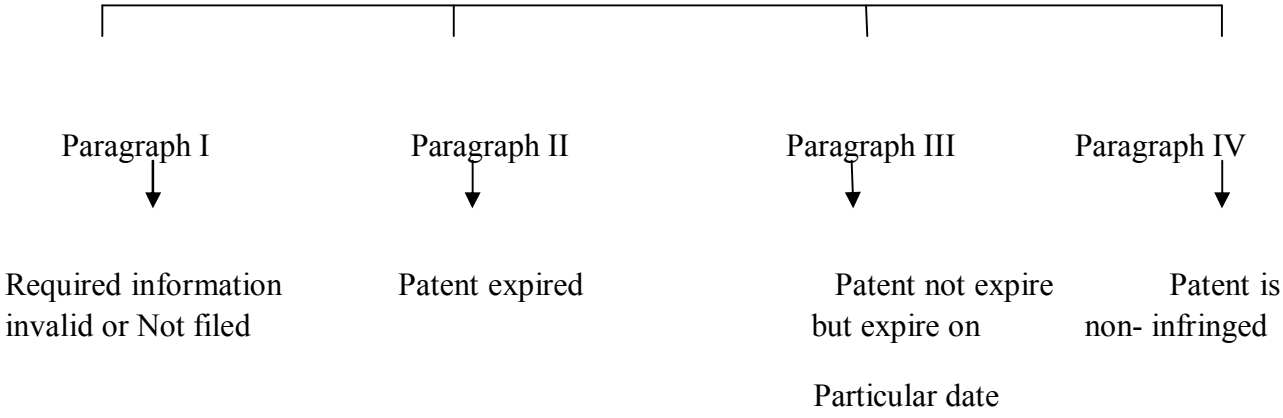
5.4 NDA Forms Used For Application: For the purpose of New Drug Application registration three major types of forms are available which are-

Form FDA-356h	Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
Form FDA-3397	User Fee Cover Sheet
Form FDA-3331	New Drug Application Field Report

6.0 ANDA[12-14]

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, and route of administration, quality, performance characteristics and intended use. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). For the approval of any generic drug product the application should be submitted to ANDA and for taking a patent on the formulation the applicant must go through the four types of paragraphs i.e Paragraph I, Paragraph II, Paragraph III, and Paragraph IV. The ANDA patent certification option chart is given below:

ANDA PATENT CERTIFICATION OPTION



6.1 Documents required for ANDA: For the filing of Abbreviated New Drug Application different types of documents are required which are listed as below:

a) Formulation:
- Bioavailability / bioequivalence
- Name of the investigator / centre
- Source of raw material and stability

b) Raw Material
- Manufacturing Method
- QC parameters, specs, stability
- Animal toxicity

c) Approval / permission for Fixed Dose Combination (FDC)
- Justification
- Pharmacokinetic / Pharmacodynamic data
- Any other data

d) Subsequent approval or approval for new indication – new dosage form
- Number and date of Approval already granted
- Justification
- Data on safety, efficacy and quality

6.2 ANDA/AADA Approved[14]

After all components of the application are found to be acceptable, an approval or tentative letter is issued to the applicant detailing the conditions of the approval and providing them with the ability to market the generic drug product. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the tentative approval of the generic drug product until the patent/exclusivity condition

has expired but a tentative approval does not allow the applicant to market the generic drug product.

6.3 The set of parameters required for NDA and ANDA Registration[12-13]

A comparison list for both NDA and ANDA common documents is listed below:

NDA Requirements (NCE)	ANDA Requirements (Generic Drug)
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

7.0 Investigational New Drug Application (IND) [15]

The vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials) is the result of a successful preclinical development program known as the investigational new drug (IND) application. the sponsor's primary goal During a new drug's early preclinical development is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development.

7.1 Generally, IND includes data and information in three broad areas:

Animal Pharmacology and Toxicology Studies	Manufacturing Information	Clinical Protocols and Investigator Information
Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans	This information is assessed as to ensure the company can adequately produce and supply consistent batches of product	Detailed protocols for proposed clinical studies to assess whether the initial phase trials will expose subjects to unnecessary risks.

7.2 Types of INDs

"Commercial INDs" are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. However, there is another class of filings broadly known as "noncommercial" INDs. The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs." During the IND review process, the medical reviewer evaluates the clinical trial protocol to determine:

1) If the participants will be protected from unnecessary risks;

2) If the study design will provide data relevant to the safety and effectiveness of the drug.

- Under Federal regulations, proposed Phase 1 studies are evaluated almost exclusively for safety reasons. Since the late 1980's, FDA reviewers have been instructed to provide drug sponsors with greater freedom during Phase 1, as long as the investigations do not expose participants to undue risks.
- In evaluating Phase 2 and 3 investigations, however, FDA reviewers also must ensure that these studies are of sufficient scientific quality to be capable of yielding data that can support marketing approval.

7.3 Phases of an investigation

1) **Phase 1:** Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. It also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.
2) **Phase 2:** Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug.
3) **Phase 3:** Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

7.4 Comparison of Drug Approval Process for New Drug Product[16]

Country	Time for Regulatory Approval of CTA* IND** Application	Time for Evaluation of MAA	MAA*** Fee
Australia	120 day	50 days	$192,400
China	50 days	180 days	DNA
India	16- 18 weeks	8-12 weeks	50,000 INR
UK	35 days	210 days	£254100
USA	30 days	180 days	$217,787

*Clinical Trial Authorization

**Investigational New Drug

***Marketing Authorization

8.0 New Drug Registration[17-19]

Under Indian law, many products which are not "new" by Western standards may still have to go through the new drug application process. The categories that require new drug registration are:

A. A drug which has not been marketed in India before.
B. A drug with a new therapeutic purpose or dosage that has not been marketed in India.
C. A new fixed-dose combination of two or more drugs, if they have not been approved in such a combination before.
D. A drug or formulation which received its first new drug approval (of any of the Types listed above) less than four years ago. This does not apply if the drug has been included in the Indian Pharmacopoeia since then.
E. Any vaccine, unless certified otherwise by the DCGI.

9.0 Documents Required For Registration of a Drug product and for Registration of a plant[20-21]

For a pharmaceutical organization to get its facility or the product registered it requires certain basic documents. The regulatory compliance of the documentation should be in accordance to ICH Q7a and 21 CFR Parts 210 and 211 of CGMP in manufacturing, processing, packing or Holding of Drugs.[21,22] Apart from various

fronts that are described in ICH Q7a and 21 CFR Parts210 and 211 of cGMP and PIC/S Guide for GMP; other important documents that are required for the purpose of registration include:

1) Master Production and Control Record (M.P.C.R)
2) Batch Production and control Record (B.P.C.R)
3) Drug Master File (DMF)
4) Site Master File (SMF)
5) Common Technical Document (CTD)
6) Annual Product Review(APR)
7) Environmental Risk Monitoring Assessment

10.0 Conclusion:

For any drug product whether it is new chemical entity or a abbreviated new drug application there are some regulatory bodies which kept an eye for their approval or for their marketing process in India or in other country. Marketing of drug products is major concern issue now days. So every country has its own guidelines and own regulatory bodies for any drug approval and for marketing of the drug products. India is emerging as an important player in the clinical research and pharmaceutical field, but to maintain this growth and to emerge as a key player on the global market, a strong and supportive regulatory framework is essential or the advantage gained so far would be lost.

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