

# **India's Marketing Regulations of Drugs**

Satish Singh, Kamal Sharma, Arun Garg

PDM College of Pharmacy, Sec-3, Bhadurgarh - 124507 (Haryana)

## **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.

## **Introduction**

During the past decade, India has been actively reforming its key industrial sectors to compete at world-class levels. Its infrastructure development, technology base creation and a wide range of production has shown tremendous progress in the Indian pharmaceutical industry. These reforms have been motivated by its expanding global trade and a self-image that has moved beyond that of a developing country. India holding fourth ranks worldwide accounting to 8% of world's production by volume and 1.5% by value. It ranks 17th in terms of export value of bulk actives and dosage forms. Indian exports are destined to more than 200 countries around the globe including highly regulated markets of US, Europe, Japan and Australia. The vast pharma market of India is being rightly celebrated in international circles for making medicines in affordable prices. The undergoing rapid shifts in other industrializing countries, India clearly recognize the need to restructure its regulatory system in order to compete the biopharmaceutical industry among international markets. According to the authors, a new regulatory structure in India is being formed, to centralize drug approvals and tighten the still somewhat lax manufacturing practices that have led to a proliferation of poor ethical practices and substandard drugs.

## **Regulatory Process:**

Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. Thus a regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is also known as drug approval process. 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.

### **Regulatory Framework- Drugs Sector**

Under the current Indian legal and regulatory regime, the manufacture, sale, import, exports and clinical research of drugs and cosmetics 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.

### **The Current Regulatory System**

The principal regulatory bodies entrusted with the responsibility of ensuring the approval, production and marketing of quality drugs in India at reasonable prices are:

**The Central Drug Standards and Control Organization (CDSCO)**, located under the aegis of the Ministry of Health and Family Welfare. The CDSCO prescribes standards and measures for ensuring the safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in the country; regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves licenses to manufacture the products.

**Drug Regulatory Authorities (DRAs)** often lacks the staff to police their respective domains. These staffing problems, combined with their relatively limited technical experience in regulatory issues, land themselves into a difficult situation. 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. 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.

## **Indian Council of Medical Research (ICMR) and Ministry of Health and Family Welfare**

The Ministry of Health, along with Drugs Controller General of India (DCGI) and Indian Council for Medical Research (ICMR) has come out with draft guidelines for research in human subjects. These GCP guidelines are essentially based on Declaration of Helsinki, WHO guidelines and ICH requirements for good clinical practice.

### **Drug Approval Process in India**

#### **New Drug Registration**

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.

#### **Approval Procedures for New Drug Application (NDA)**

In India there is no requirement for any registration of a drug. However, there is a need for approval from the Drug Controller General of India (DCGI) to import, market, or manufacture a “new drug.” All new drugs (drugs not previously used in India or in use for less than four years) proposed to be introduced must be approved for import or manufacture in India by the DCGI. The application for permission to import or manufacture must be accompanied by the appropriate dossier as follows.

#### **The full set of data to be submitted consists of:**

##### **A. Permission to market new drug application (NDA)**

1. Chemical and Pharmaceutical information
2. Animal Pharmacology
3. Animal Toxicology
4. Human / Clinical Pharmacology
5. Exploratory Clinical Trials
6. Confirmatory Clinical Trials
7. Bioavailability / dissolution and stability data

8 Regulatory status in other countries

9. Marketing information:

(a) Proposed product monograph

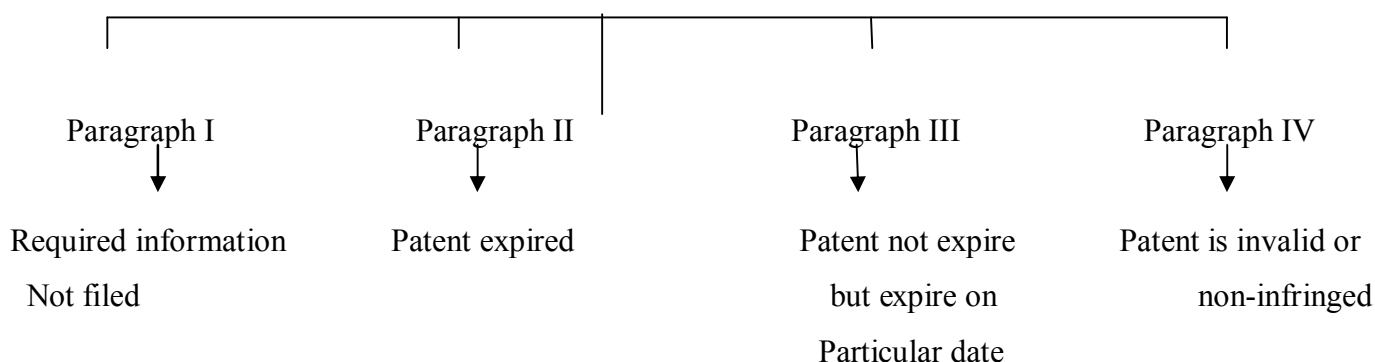
(b) Drafts of labels and cartons

10. Application for test license

## **B. Subsequent approval / permission for manufacture of already approved new drug application**

**(ANDA):** 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**



### **Documents required for ANDA:**

#### **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

All items above may not be required for all drugs. In case the drug is already approved and marketed abroad, then only Phase III trials may be required in India. Further, such trials would need to be conducted on at least 100 persons spread over 3-4 locations in the country. However, the DCGI may agree to dispense with the need for local clinical trials, if it is in the public interest and if it can use the data of trials carried out in other countries. Similarly, the submission of data related to animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity may be relaxed or modified in case the drugs are in use overseas for several years and there is adequate published evidence regarding the safety of the drug.

Permission from the DCGI has to be obtained to import samples for clinical trials and to carry out the clinical trials in India.

In case the new drug is a fixed dose combination (FDC) of existing approved active ingredients which are merely being combined for convenience and provision of a stable acceptable dosage form, then no additional animal or human data are generally required and marketing permission may be granted if the FDC has an acceptable rationale whereas if the combination is being done for the first time, and a claim is being made, and/or the combination is likely to result in a significant interaction of a pharmacodynamic or pharmacokinetic nature, then it is treated in the same way as any other new drug.

The period to take approval for a new drug is not possible to estimate, and the law lays down no time limit. However, it can be assumed that after the submission of the full (final) dossier, it may take around three months, though this is only an estimate. The actual time taken depends on the amount and effectiveness of follow-up that is done by the local agent with the concerned authorities.

**Comparison of Drug Approval Process for New Drug Product**

<b>Country</b>	<b>Time for Regulatory Approval of CTA* IND** Application</b>	<b>Time for Evaluation of MAA</b>	<b>MAA*** Fee</b>
----------------	---	-----------------------------------	-------------------

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

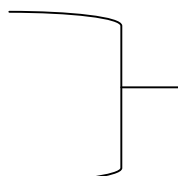
**The set of parameters to be required for NDA and ANDA Registration:** For the approval of new chemical entity the application to be submitted for NDA and for a approval of a generic drug product the application should be submitted for ANDA. A comparison list for both NDA and ANDA common documents is listed below:

#### **NDA Requirements (NCE)**

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

#### **ANDA Requirements (Generic Drug)**

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence



**Note:** From the above comparison list it is observed that there is fewer documents are to be required for the generic drug product approval so this is the reason that generic drug products are cost effective.

### **New Drug Approval Process**

#### **Clinical Trials**

Each year many new prescription drugs are approved by the Food and Drug Administration (FDA). The process of developing and bringing new drugs to market is important to understand by the primary care physicians. The process initiates with preclinical testing. For drugs that appear safe, an investigational new drug application is filed with the FDA. If approved, clinical trials begin with phase 1 studies that focus on safety and pharmacology.

Phase 2 studies examine the effectiveness of the compound. Phase 3 is the final step before submitting a new drug application (NDA) to the FDA. An NDA contains all the information obtained during all phases of testing. Phase 4 studies or post marketing studies, are conducted after a product is approved. Recent changes in legislation have streamlined the approval process. Critics contend that these changes have compromised public safety, resulting in the need to recall several products from the market. Proponents claim that changes in the approval process help patients with debilitating diseases, such as acquired immune-deficiency syndrome, that were previously denied critical medication because of bureaucratic regulations. (J Am Board Fam Pract 2001;14:362–7).

### **FDA Approvals**

Once a company develops a drug, it undergoes around three and a half years of laboratory testing, before an application is made to the U.S. Food and Drug Administration (FDA) to begin testing the drug in humans. Only one in 1000 of the compounds that enter laboratory testing will ever make it to human testing.

If the FDA gives the green light, the "investigative" drug will then enter into the following three phases of clinical trials:

- Phase 1 uses 20-80 healthy volunteers to establish a drug's safety and profile. (about 1 year)
- Phase 2 employs 100-300 patient volunteers to assess the drug's effectiveness. (about 2 years)
- Phase 3 involves 1000-3000 patients in clinics and hospitals who are monitored carefully to determine effectiveness and identify adverse reactions. (about 3 years)

The company then submits an application (usually about 100,000 pages) to the FDA for approval, a process that can take up to two and a half years. After final approval, the drug becomes available for physicians to prescribe. At this stage, the drug company will continue to report cases of adverse reactions and other clinical data to the FDA.

The research-based pharmaceutical industry currently invests some US\$12.6 billion a year in new drug development. Historically, the drug development figure doubles every five years.

### **Important Documents Required For Registration of a Drug product**

For a pharmaceutical organization to get its facility or the product registered it requires certain basic documents. Usually requirements of documentation depend on the country in which the facility or product is to be registered. But compliance with ICH Q7a usually facilitates the approval or licensing of the organization.

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.<sup>21,22</sup> Apart from various fronts that are described in ICH Q7a and 21 CFR Parts 210 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

### **Drug Master File (DMF)**

A DMF is a submission to Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in manufacturing, packaging and storing of one or more human drugs. The submission of DMF is not required by law or FDA regulations. A DMF is submitted only at the discretion of the holder only. The information in DMF may be used to support and investigational New Drug Application (IND), a new Drug Application (NDA), an Abbreviated New Drug Application (ANDA). There are five types of DMFs:

Type I: Manufacturing Site, Facilities, Operating Procedures

Type II: Drug Substances, Drug Substance Intermediate and Material Used in DMF; their production or Drug Product.

Type III: Packaging Materials

Type IV: Excipient Colorant, Flavor, Essence or material used in their preparation

Type V: FDA Accepted Reference Information

DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF.<sup>23</sup>

### **Site Master File (S.M.F)**



Site master File is a document in pharmaceutical industry which provides information about the production and control of manufacturing operations. The document is created by a manufacturer and contains particular information about the quality assurance, quality control of pharmaceutical manufacturing operations carried out by the named site.

The purpose of S.M.F is to provide the complete information about the company activities prior to the inspection. It also serves as foundation document for the company onto which other information can be based for the success of the company unit operations.

### **Common technical Document (C.T.D)**

The International Conference of Harmonization (ICH) process has achieved a significant harmonization in technical requirements or registration of pharmaceuticals for human use in three ICH regions- United States, Europe and Japan. The ICH M4 Guidelines describes an acceptable format and contents for a Common Technical Document suitable for submission to regulatory authorities in the three ICH regions once supplemented with regional administration particulars.<sup>24</sup>

### **The CTD consist of five modules:**

Module I: Regional Administrative Information

Module II: IIA Executive summaries

IIB Non clinical summaries

IIC Clinical summaries

Module III: Quality

Module IV: Non clinical Data Study Report

Module V: Clinical Data Study Report

The CTD as defined by the M4 Expert Working Group does not cover the full submission that is to be made in a region.

### **Environmental Monitoring Risk Assessment**

Environmental monitoring describes the microbiological testing undertaken in order to detect the changing trends of microbial counts and micro flora growth within clean room on controlled Environment. The two most commonly used methods for environmental monitoring are Hazard Analysis and Critical Control Point (HACCP) and Failure Mode and Effect Analysis (FMEA).

### **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.

## References:

1. <http://cdsco.nic.in/html/Copy%20of%201.%20D&CAct121.pdf>
2. <http://cdsco.nic.in/index.html>
3. Wong, J. et al. "Harnessing the Power of India," BCG Focus, May 2006, accessed 26 Dec 2007.
4. <http://www.drugs.com/fda-approval>
5. <http://www.fda.gov/InternationalPrograms/Agreements/ucm131179.htm#asiapac>
6. <http://cdsco.nic.in/index.html>
7. Subbi Reddy, K. "How Drugs Regulatory System in India Should Be?" Pharmabiz (27 Aug 2003)
8. Vinod Sople, 'Legal Aspects of Marketing in India', New Age Publications, New Delhi, 2004
9. Gehl Sampath, Padmashree. 2008. 'India's Pharmaceutical Sector in 2008. Emerging Strategies and Global and Local Implications for Access to Medicines'.
10. OPPI. 2008. Indian Pharmaceutical Industry: Vision 2015.
11. Singh, Seema. 2007. 'Indian Pharma enters the global arena'. Cell. 128 March 9. Elsevier
12. Srivastava, D. 2008. 'A Country level report on the pharmaceutical sector in India'. Report commissioned by DFID, UK.
13. Meadows, M. The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective (2002).[http://www.fda.gov/fdac/features/2002/402\\_drug.html](http://www.fda.gov/fdac/features/2002/402_drug.html) (assessed on December 14th 2009).
14. Lipsky M.S. and Sharp L.K., "From Idea to Market: The Drug Approval Process" J Am Board Fam Pract. 2001; 14:362–367.
15. Martinez L.J., "FDA Overview: An Overview of the Drug Approval Process" Research Initiative Treatment Action (RITA), 2002: 8.
16. Kumar S., Drug Approval Process- USA vs. INDIA (2010) <http://www.pharmainfo.net/santosh-kumar-jh/drug-approval-process-usa-vs-india>. (assessed on May 16th 2010)
17. <http://cdsco.nic.in/CDSCO-GuidanceForIndustry.pdf>. (Assessed on February 24th 2010).
18. The Drugs and Cosmetics Acts 1940 and Rules 1945. Page no. 156-161 <http://cdsco.nic.in/html/Copy%20of%201.%20D&CAct121.pdf> (assessed on May 21<sup>st</sup> 2010)
19. Australian Regulatory Guidelines for Prescription Medicines (ARGPM)-2003 <http://www.tga.gov.au/pmeds/argpm.htm>. (Assessed on October 8<sup>th</sup> 2009).
20. USP-India, "Quarterly Update" (Oct 2007)
21. GMP Guide for API-Q7a, ICH Harmonized Tripartite Guidelines, ICH Expert Working Group, Step 4 Version 2000;12-6.

22. 21 CFR Parts 210 and 211, Current Good Manufacturing Practice in Manufacturing, Processing, Packaging or Holding of Drugs, General and Current Good Manufacturing Practice for Finished Product, 2006.
23. Guidelines For Drug Master File, FDA, CDER, Office of Drug Evaluation, Maryland, United States, 1989.
24. Common Technical Document Specification, M-2 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999; 2-5