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Review Article

REGULATORY DOSSIER SUBMISSION IN INDIA

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ABSTRACT

Drug Regulatory Authority is defined as an authority appointed by the government to administer the granting of marketing authorization/approval of pharmaceutical products and biologicals in a country. It is also called as the Licensing Authority or Marketing Authority. The Drug Regulatory Authority of India is the Central Drugs Standard Control Organization (CDSCO), under the Ministry of Health and Family Welfare (MOHFW). Pharmaceutical Dossier of India is the major document required for the process of marketing approval of the pharmaceutical products and biologicals in India. Its content and format follows the Common Technical Document (CTD) as set out by the International Conference on Harmonization (ICH). The CTD of India is organized into 5 Modules. The information required under each module is suitably detailed in this article.

Keywords: *CDSCO, CTD, India, Pharmaceutical Dossier, Pharmaceutical product, Module*

INTRODUCTION

Many new pharmaceutical products have flourished and trade in the pharmaceutical industry has taken on an international domain. At the same time, however, the circulation of adulterated, substandard and counterfeit drugs on the national and international market has increased. Therefore, there is a strong need for improvement in the approval process of a new drug, demonstration of its safety, efficacy and quality before it could be approved for commercialization in the market. All of these problems can be tackled effectively only by establishing an effective drug regulatory system. Drug Regulation is defined as the totality of all the measures - legal, administrative and technical which the Government takes to ensure the safety, efficacy and quality of drugs, as well as the relevance and accuracy of product information [1]. The development, production, importation, exportation, distribution and registration/approval of the drugs must be regulated via a proper channel to ensure that they meet the required prescribed standards.

Every country has its own Drug Regulatory Authorities, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of a drug. Therefore, it is very difficult, especially for the companies with global approach to develop one single regulatory approach for a Marketing Authorization Application (MAA) for a new drug on the basis of one dossier submitted simultaneously to different countries in the world. It is very important to know in detail and exactly the regulatory requirements in each concerned country where a Registration Dossier should be submitted to establish a suitable regulatory strategy before

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the submission in order to avoid any major difficulties [2].

The integration of all the data of a new pharmaceutical product ranging from its procurement data to preclinical and clinical studies in a proper format and content in the pharmaceutical dossiers filed by the manufacturer/applicant of such a new drug to the Regulatory Authorities of the respective countries for its approval for sale and commercialization in the market is a promising solution to ensure early, safe and efficacious supply of the drugs to the patients. The 'Pharmaceutical Dossier' is defined as the collection of documents of all the relevant information of a pharmaceutical product to be submitted by the drug sponsor/applicant/manufacturer to the Drug Regulatory Authority of a country for its approval/registration for sale and commercialization in that market.

PHARMACEUTICAL DOSSIER

Pharmaceutical dossier of a pharmaceutical product is also called as Registration Dossier, Product Licensing Application, Marketing Authorization Application, Marketing Approval Application and New Drug Application (NDA) or simply as Dossier [3] is the most important aspect in the approval of a product before its marketing in a particular country.

The information to be submitted in a dossier includes its-

- Administrative documents like the application forms, labels, package inserts etc.
- Chemistry, Manufacturing and Characterization (CMC) data of the Drug Substance (DS) and Drug Product (DP)
- Pre- clinical data (animal studies data)
- Clinical data (human studies data)

The aim of the dossier is to provide enough information to permit Regulatory Agencies' reviewers to establish that - the drug has quality, efficacy and safety properties suitable for the intended use, the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity, the benefits of the drug outweigh its risks and it carries a suitable label and packet insert for use by the patients [4].

The Pharmaceutical Dossier is divided into various parts called as 'modules'. Each module contains specific information about the pharmaceutical product. The Numbers of the module, name of the module and the content the module for the Pharmaceutical Dossier varies from country to country. For example, the Pharmaceutical Dossier of India and USA has 5 modules while the dossier of Association of South-east Asian Nations (ASEAN) has 4 modules [5]. Dossiers can extend to thousands of pages of data and information that must be analyzed by the Drug Regulatory Agencies seeking evidence that the product meets their quality, safety and efficacy requirements. This process is technically challenging, with the difficulty increasing from simple generic drugs, to new formulations and fixed dose combinations (FDCs), while novel drugs and biological products such as vaccines are the most difficult of all to assess.

REGULATORY FRAMEWORK OF INDIA

In India, under the Drugs and Cosmetics Act, the regulation of manufacture, sale and distribution of drugs is primarily the concern of the State Authorities while the Central Authorities are responsible for the approval of new drugs, clinical trials in the country, laying down the standards for drugs, control over the quality of imported drugs, coordination of the activities of various State Drug Control Organizations and to provide expert advice with a view to bring about uniformity in the enforcement of the Drugs and Cosmetics Act, 1940 and Rules, 1945. At the Central level, the main Regulatory Authority in India is the Central Drugs Standard Control Organization (CDSCO), under the Ministry of Health and Family Welfare (MOHFW) which is responsible for approving new drugs, clinical trials, and licensing of drugs.

The Headquarter of CDSCO is located at FDA Bhawan, Kotla Road, New Delhi 110002 and functions under the Directorate General of Health Services (DGHS). The The Drug Controller General of India (DCGI) is the main personality of CDSCO responsible for approving new drugs, clinical trials, licensing and to ensure quality, safety and efficacy of pharmaceuticals in India. Presently, Dr. G. N. Singh is serving as DCGI of India [6].

Major Rules of Drugs & Cosmetics Rules, 1945 Involved in Dossier submission in India

The Rules 122A, 122B and 122D, 122 DA, 122E of Drugs and Cosmetics Rules and Appendix I, IA and VI of Schedule Y, describe the information/data required for approval of clinical trial and/or to import or manufacture of new drug for marketing in the country. These rules are explained below:

Rules 122A: It explains the format of application for permission to import New Drug by an applicant to be submitted to the Drug Regulatory Authority of a country.

Rules 122B: It explains the format of application to be submitted to the Drug Regulatory Authority of a country for approval to manufacture New Drug other than the drugs classifiable under Schedules C and C (1) by an applicant.

Rules 122 D: It is concerned about the permission granted to the applicant to import or manufacture fixed dose combination by the Drug Regulatory Authority of a country.

Rules 122DA: It highlights the application for permission to conduct clinical trials for New Drug/Investigational New Drug by an applicant to the Drug Regulatory Authority of a country.

It should be made in Form 44 and accompanied by the duly fees as prescribed by the CDSCO for the various phases of the trials. For Phase-I clinical trials, also called as human clinical trials on a new drug , a fee of fifty thousand rupees is required to be submitted along with the application form and data as prescribed in Schedule Y. For Phase-II clinical trials, also called as Exploratory clinical trials and Phase-III clinical trials, also called as Confirmatory clinical trials, a fee of twenty-five thousand rupees is to be submitted.

Rules 122E: This explains the definition of a "new drug" in India. It is defined as a drug, including bulk drug substance, which is not recognised as effective and safe by the Central Licensing Authority for the expected claims or which is not used in India to any significant extent under the prescribed conditions, recommended or suggested in the labelling thereof or an already approved drug with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration or an already approved fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in a marketed combination is proposed to be changed, with certain claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration;

FORMAT AND CONTENT OF THE DOSSIER

The Drug Regulatory Agencies have established a proper content and format for filing of dossiers by the drug applicant. By this, the required information is arranged in a specific format and sequence which lead to ease of reference and search of information and facilitates easy and early review process as the reviewers can quickly ascertain which information is missing and the required information can be efficiently located. This in turn facilitates continued public access to safe, efficacious and good quality essential drugs

In India, CDSCO adopts Common Technical Document (CTD) format for technical requirements for registration of pharmaceutical products for human use. The same is already in use for biological products since February 2009. This guidance is developed by CDSCO based on International Conference on Harmonization (ICH) Harmonized Tripartite Guideline on

"Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use". M4, Step 4 version dated January 13, 2004 and Drugs & Cosmetics Act 1940 and Rules made there under. The complete name of ICH is the "International Conference on harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use". ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines [7, 8].

The CTD of India is organized into five modules (Module 1, 2, 3, 4, and 5) as shown in the Figure 1.

Module 1: General Information
Module 2: CTD Summaries
Module 3: Quality
Module 4: Nonclinical Study Reports
Module 5: Clinical Study Reports

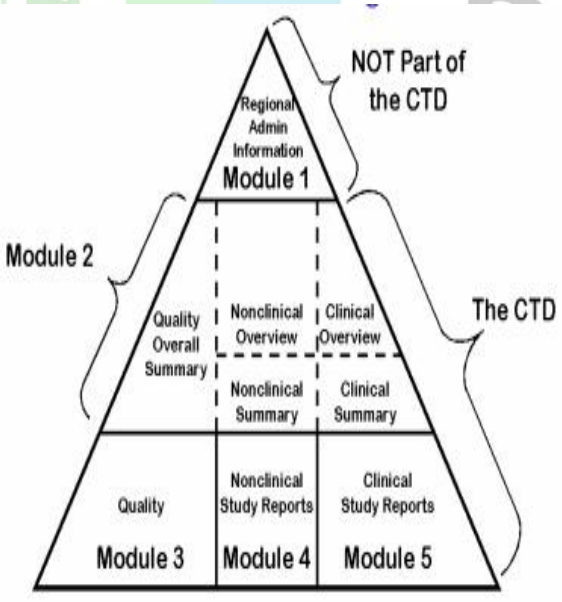

Figure1; CTD Of India

The following instructions should be followed for the regulatory dossier submission of a pharmaceutical product for marketing in India-

- The display of information should be unambiguous and transparent throughout the dossier.
- Text and tables should be prepared using margins that allow the document to be printed on both A4 paper
- The left-hand margin should be sufficiently large that information is not obscured by the method of binding.
- Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying.
- Times New Roman, 12-point font is recommended for descriptive text and Times New Roman, 9 to 10-point font for table contents and text.
- Every page should be numbered, according to the granularity document.
- Acronyms and abbreviations should be defined the first time they are used in each module.
- References should be cited in accordance with the current edition of the Uniform `Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE).

CTD of India

Module 1: General Information

The Module 1 of CTD of India is named as "General Information". It basically contains the various application forms issued for seeking permission from DCGI during the drug development process and the licenses granted by the CDSCO for the same. The major document required in India for the registration purpose to CDSCO is the Form 44. Form 44 is the application made to the DCGI for import or for manufacture a new drug or undertakes clinical trials.

For import and marketing of finished products, Form 11, Form 20 B / 21 B, Form 29, Free Sale Certificate (FSC) and/or Certificate of Pharmaceutical Products (CPP) are additionally required. Form 11 is the license issued by the DCGI for the import of drugs for test or analysis. Form 20 B is the license granted to sell by wholesale drugs other than schedule C, C (1) and X drugs. Form 21 B is the license granted to sell by wholesale drugs included in schedule C, C (1) excluding schedule X drugs. Form 29 is the license

granted to manufacture drugs for the purpose of examination, test or analysis. Free Sale Certificate (FSC) of a pharmaceutical product is a document stating that this product is freely sold in the country of origin without any restrictions. Certificate of Pharmaceutical Products (CPP) is a document which establishes the status of the pharmaceutical product and of the applicant in the exporting country.

For manufacture and marketing of finished products, Form 25/ 28/ 26 and Form 29 are to be attached along with the dossier additionally. Form 25 is the license granted to manufacture drugs other than schedule C, C (1) and X drugs. Form 28 is the license granted to manufacture drugs included in schedule C, C (1) excluding schedule X drugs. Form 26 is the license granted to manufacture drugs other than schedule X drugs. Form 29 is the license granted to manufacture drugs for the purpose of examination, test or analysis.

The format of Module 1 of CTD of India is as follows-

Covering Letter & Comprehensive Table of Contents (Modules 1 to 5)

Administrative Information

- Brief introduction about the applicant company
- Duly filled and signed application in Form 44 and Treasury Challan

For import and marketing of finished products

- Copy of drug sale license in Form 20B / 21B
- Copy of Free Sale Certificate (FSC) and/or Certificate of Pharmaceutical Products (CPP) issued by the Regulatory Authority of the country of origin / free sale certificate issued by the Regulatory Authorities of other major countries.
- Batch release certificate
- Copy of Form 11 for imported drug product for testing purpose

For manufacture and marketing of finished products

- Copy of existing manufacturing license in Form 25 /28 / 26
- Copy of Form-29

Coordinates related to the application

Name, address, telephone, fax, e-mail of applicant of drug product, manufacturer of drug substance, other manufacturer involved in the production process, official responsible for releasing batches of drug product, authorized agent in India: (for imported drug products)

General Information on Drug Product

- Product Labelling: Proposed draft labels and cartons have to be provided.
  - Primary package label
  - Secondary package label
- Summary of the packaging procedures

Summary of Testing Protocol(s) for Quality Control Testing

Regulatory status in other countries

Domestic price of the drug followed in the countries of origin in INR

Samples of drug product

Promotional materials

Module 2: CTD Summaries

This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, not exceeding one page.

Module 2 should contain 7 sections in the following order:

CTD table of contents
CTD introduction
Quality overall summary
Nonclinical overview
Clinical overview

Nonclinical written and tabulated summaries
Clinical summary

Module 3: Quality

Information on Quality should be presented in the structured format in Module 3 as described below:

- Table of Contents of Module 3
- Body of Data

Drug substance(s)

- General Information
- Manufacture of Drug Substance (name, manufacturer)
- Characterization of Drug Substance (name, manufacturer)
- Quality Control of Drug Substance (name, manufacturer)
- Reference Standards or Materials (name, manufacturer)
- Container Closure System (name, manufacturer)
- Stability of Drug Substance (name, manufacturer)

Drug product (name, dosage form)

- Description and Composition of the Drug Product (name, dosage form)
- Pharmaceutical Development (name, dosage form)
- Manufacture of drug product (name, dosage form)
- Controls of Excipients (name, dosage form)
- Control of Drug Product (name, dosage form)
- Reference Standards or Materials (name, dosage form)
- Container Closure System (name, dosage form)
- Stability (name, dosage form)

Appendices

- Facilities and Equipment (name, manufacturer)
- Adventitious Agents for Safety Evaluation (name, dosage form, manufacturer)
- Excipients

Module 4: Nonclinical study reports

The nonclinical study reports should be presented in the order described below:

- Table of contents of module 4
- Study reports
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
    - Genotoxicity
    - Carcinogenicity
    - Reproductive and Developmental Toxicity
    - Local Tolerance
    - Other Toxicity Studies

Module 5: Clinical study reports

The human study reports and related information should be presented in the order described below:

- Table of contents of module 5
- Tabular listing of all clinical studies

Clinical study report

- Reports of Biopharmaceutical Studies
- Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
- Reports of Human Pharmacokinetic Studies

- Reports of Human Pharmacodynamic Studies
- Reports of Efficacy and Safety Studies
- Reports of Post - Marketing Experience
- Case Report Forms and Individual Patient Listings [9-11]

Therefore, every applicant who wishes to commercialize its pharmaceutical products in India should file its data in the above format. This will not only save time, money but also lead to reduced submission and approval time of the dossier.

Regulatory Initiatives-

Inspite of various Committees and guidelines formed for the regulatory streamlining of drugs in India, the Indian market is still far behind those of the developed countries. Some of the initiatives to strengthen it are listed below-

- There is a need to establish an integrated regulatory system through the constitution of a National Drug Authority so that regulation of quality and price control is performed by the same agency.
- Pharmacovigilance centres at national, zonal and regional levels to monitor adverse drug reactions should be set up.
- Capability strengthening to monitor clinical trials, including the setting up of the Clinical Trials Registry of India (CTRI) should be done.
- Description of The Over the Counter (OTC) Drug legislation, Accelerated Approval, Fast Track, Priority Review in Drugs and Cosmetics Act 1940 and Rules, 1945.
- The Central Government should create additional posts for uniform and effective implementation of Drugs and Cosmetics Act and Rules thereunder.
- CDSCO Training Academy for updating knowledge and skills of the regulatory officials should be established.
- Various APIs are imported into India for manufacturing drug formulations. CDSCO should carry out overseas inspections of the manufacturing units
- With increased globalization of the regulatory mechanism apart from the changing profile of the pharmaceutical industry, it is important to impart continuous training to the drug regulators.

CONCLUSIONS

Every country has its own Drug Regulatory Authorities, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of a drug. It is very important to know in detail and exactly the regulatory requirements in each concerned country where a Registration Dossier should be submitted to establish a suitable regulatory strategy before the submission in order to avoid any major difficulties. In India, the pharmaceutical dossier should be in accordance with the CTD format of India.

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REFERENCES

1. *Dureja H. New Drug Approval Process: Regulatory Review. http://www.pharmainfo.net/reviews/new-drug-approval-process-regulatory-view 27 July. 2015.*
2. *Ratanawijitrasin S, Wondemagegnehu E, In: Effective drug regulation A multicountry study. http://archives.who.int/tbs/qual/s2300e.pdf (17 June. 2015).*
3. *Marketing authorization. Wikipedia.org. 29 May.2015 http://en.wikipedia.org/wiki/Marketing_authorization (19 June. 2015).*
4. *New drug application (FDA). Wikipedia.org. 16 June.2015 http://en.wikipedia.org/wiki/New_Drug_Application (19 June. 2015).*
5. *Association of Southeast Asian Nations. Wikipedia.org. 22 June. 2015 https://en.wikipedia.org/wiki/Association_of_Southeast_Asian_Nations(25 June. 2015).*
6. *Patel M., Patel K., An overview to CTD, ACTD and Indian Requirements for Dossier Submission: Differences and Similarities, Indo American Journal of Pharmaceutical Research. 2015; 3 :2: 1746-51.*
7. *M4: The Common Technical Document. ich.org. http://www.ich.org/products/ctd.html (25 June. 2015).*

8. *History-The need to harmonise, Initiation of ICH and Evolution of ICH. ich.org. http://www.ich.org/about/history.html (25 June. 2015).*
9. *Central Drugs Standard Control Organization (Import and Registration Division) Guidance Document. cdsco.nic.in. 5 July. 2015*

www.cdsco.nic.in/writereaddata/Guidance%20documents.pdf (5 July. 2015).
10. *Guidance for Industry on Submission of Clinical Trial application for Evaluating Safety and Efficacy. Cdsco.nic.in. 10 July. 2015 www.cdsco.nic.in/writereaddata/CDSCO-GuidanceForIndustry.pdf (10 July. 2015).*
11. *Guidance for Industry on the Preparation on Common Technical Document for import/manufacture and marketing approval of new drugs for human use (New Drug Application – NDA). Cdsco.nic.in. 19 July. 2015 http://www.cdsco.nic.in/writereaddata/CTD%20Guidance%20Final.pdf (19 July. 2015).*