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Review Article



Drug approval process in India and Europe

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Abstract

Every time a new drug is developed it requires a great amount of research work in manufacturing, Pre-clinical Science, Controls, Chemistry & Clinical trials. Regulatory agencies have Drug Reviewers who has the responsibility of checking that whether the data supports the Safety, Effectiveness and Quality control of a New Drug product to serve the public health. Every country has its own Regulatory agency which is responsible for regulating all the Rules and Regulations and forms the guidelines for regulating the Manufacturing, Processing and Marketing of the Drugs. This Article focuses on Drug Approval Process in Europe and India.

Keywords: Drug approval, Clinical Trial, MAA, CDSCO, Centralized procedure, Mutual recognition procedure, Decentralized procedure, National procedure

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1. Introduction

At present every country has its own set of rules and regulations for the approval of new drug. For the marketing authorization procedure in each country applying a single process is not possible, so it is necessary to have knowledge of marketing authorization procedure of each and every country.

2. EUROPE – Drug approval process (1)

Before a drug is marketed in European Union, there are two steps which are to be fulfilled -:

- Clinical Trial Application and
- Marketing Authorization application(MAA)

European Union consists of 28 Member states. Clinical trial applications are approved only at Member state level and MAA can be approved at both central and state level.

There are 4 types of procedures by which a drug gets approval in European Union:-

- Centralized procedure

- Mutual recognition procedure

- Decentralized procedure &

- National procedure

a) Centralized Procedure – This is the centralized procedure which provides applicant the market authorization which is valid throughout the European Union.

This authorization is valid in European Union, Norway, Iceland and Liechtenstein. Application is evaluated by an assigned Registrar, then EMA issues their opinion in 210 days and the application is further submitted to the European Commission for the final approval.

Centralized Procedure is compulsory for the medicines of Cancer, Diabetes, Auto-immune disease, for Orphan medicines. The following flow chart describes the approval process by centralized procedure.

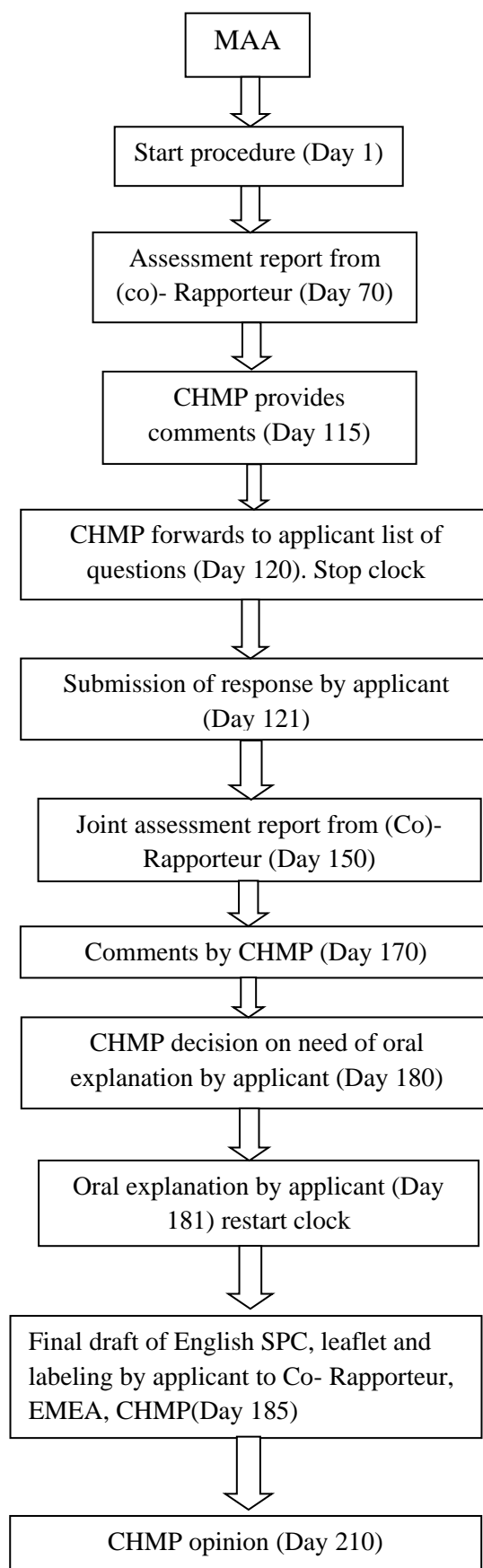


Figure 1. Centralized Procedure

b) Mutual Recognition Procedure - The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the concerned member states

(CMS) other than the Reference member state (RMS), where the drug is previously approved. Applicant has to submit a Dossier to all the European Union Member

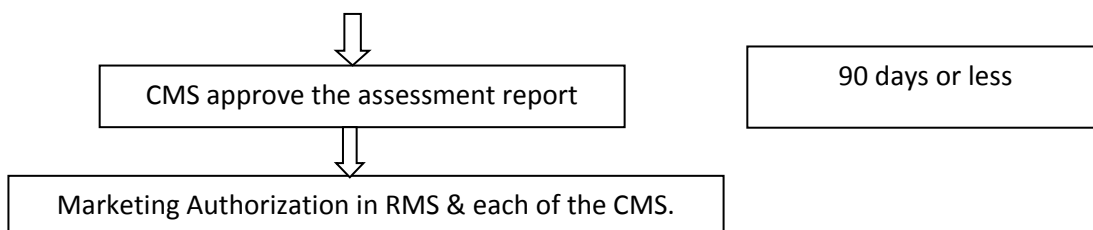


Figure 3. Decentralized Procedure

d) **Nationalized Procedure** – In this procedure the applicant is allowed to obtain a marketing authorization in any of the one member states. To get the National Marketing authorization, the applicant needs to submit the

application to the competent authority of the member state; new active substance can also obtain marketing authorization under this procedure. This whole process may take time period up to 210 days.

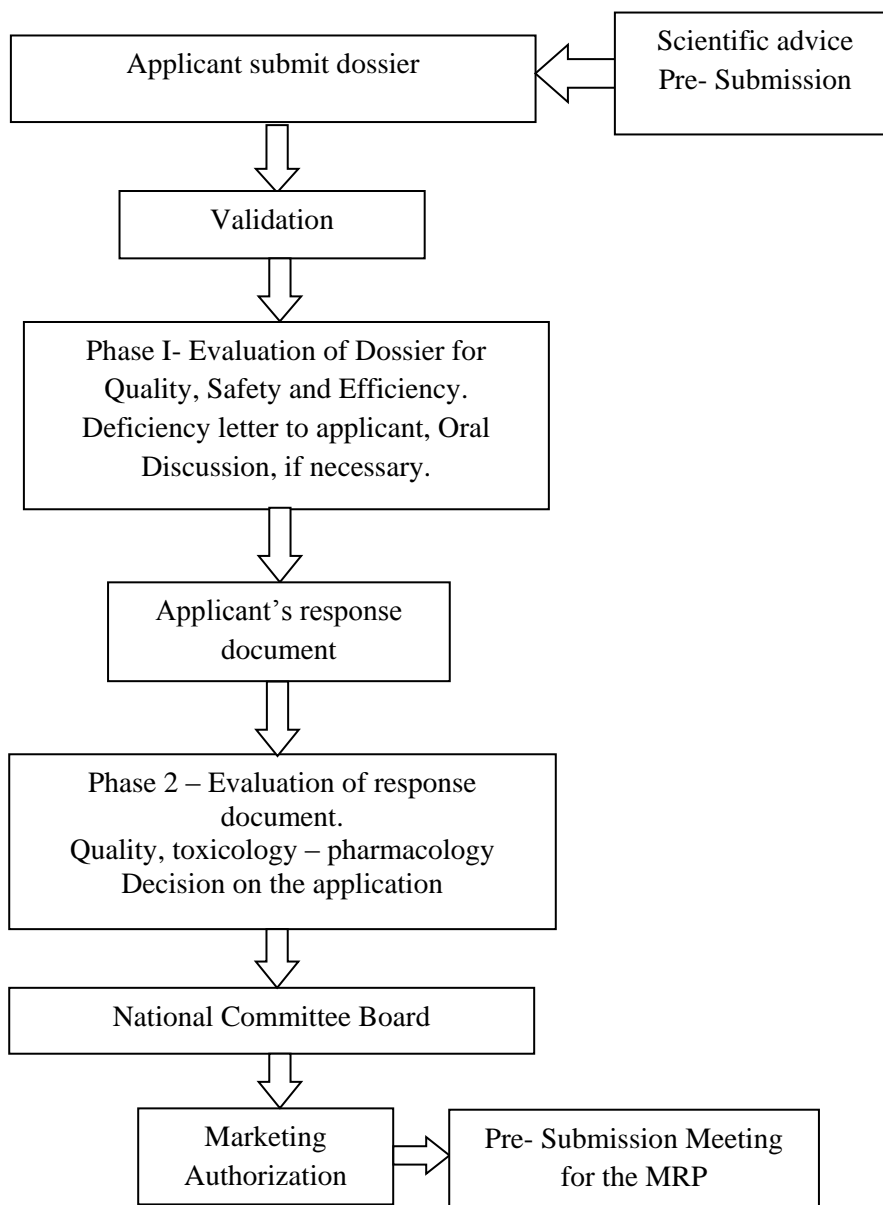


Figure 4. National Procedure

3. Submission of Marketing Authorization Application (2)

While preparing the application submission of marketing authorization, the applicant has the chance to

meet the EMEA and discuss any issues facing on the proposed submission, and for scheduling the meeting with EMEA the applicant should send a request to EMEA using the "Pre-Submission meeting request form" which is included in Pre-submission guidance document.

Pre-Submission Meeting (2)

Applicant should notify EMEA at least 7 months before, submitting the application. The notification should include:-

- i. Product characteristics summary
- ii. Pharmaceutical forms/ pack sizes

Selection of Rapporteur/ Co-Rapporteur (3)

A Rapporteur or a Co-Rapporteur is appointed for any type of scientific evaluation. A Rapporteur does the evaluation and prepares an assessment report to the CHMP. Request for appointment of Rapporteur/Co-Rapporteur should be provided 7 months before submission date, and 2 weeks before to EMEA, in advance of CHMP meeting.

Submission of Application (3)

Applicant and EMEA should decide and arrange the date and time of delivery of the dossier to the EMEA. EMEA will inform further to the applicant in advance of the meeting scheduled with the CHMP so they can identify the submission dates.

If in any case, the applicant finds that, he can't submit the application on the submission date, and then the applicant should inform the EMEA and the Rapporteur /Co-Rapporteur in advance.

Dossier to be submitted (3)

Applicant need to submit the following documents to the EMEA:-

- i. One copy of the dossier from 1 to 5 modules in eCTD format, including Active substance master file's Applicant's part, if any
- ii. Additional 2 copies of module 1 and 2
- iii. Summary report of product characteristics, labeling and package leaflet in English

Applicant should submit the dossier both to Rapporteur/Co-Rapporteur and EMEA

Validation by EMEA (3)

During the validation process EMEA product team lead consults the Rapporteur on the matters such as GMP inspection, GCP inspections and completeness of data, and if they need any additional information they can contact the applicant requesting the supply of data.

Outcomes of the Validation (4)

1. **Positive outcome** – If positive outcomes come, EMEA shall notify the applicant in written that

validation is successfully completed, and will also send the name of CHMP members to whom full or partial copies of the dossier should be sent.

2. **Negative outcome**- Negative outcome happens if the applicant fails to provide the data, information or clarification if any requested or fails to adhere to the EU CTD format.

The applicant is informed in writing by the EMEA and is told either to collect the dossier or have it destroyed by the EMEA.

Inspection Report (4, 5)

The Inspector makes a report with comments on the major errors within 15 days. Within 180 days the final report is sent to EMEA inspection section and is circulated to the Rapporteur and Co-Rapporteur and CHMP.

4. Approval of New Drug in India (6-9)

If any company in India wants to manufacture or import a new drug, they need to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. To prove its efficacy and safety in Indian population they need to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.

There's a provision in Rule-122A of Drug and Cosmetic Act 1940 and Rules 1945, that if the licensing authority finds out that if everything is in the interest of public health then he may allow the import of new drugs, based on the data of the trials done in other countries.

Another provision is Rule-122A is that clinical trial may be allowed in any new drug case, which are approved and already being used for many years in other countries.

Section 2.4(a) of Schedule Y of Drug and Cosmetic Act 1940 and Rules 1945 says for every drug which is discovered in India, will undergo all the phases of clinical trials.

Section 2.4 (b) of Schedule Y of drug and cosmetic act 1940 and rules 1945 says for all the drugs which are undiscovered outside or in other countries except India, the applicant should submit all the documents or data from their or other countries or the other licensing authority may require the applicant to repeat all the studies or may provide a choice to proceed from phase 3 clinical trial.

On overall, the exact requirements of the clinical trials keep on changing from case to case and also depend upon the satisfaction level of licensing authority about the safety and efficacy profile.

All though the approval process of new drug in India is very complicated process, so it should meet necessary requirements related to NDA to FDA.

The figure below show the approval process in INDIA

Drug approval process in India:

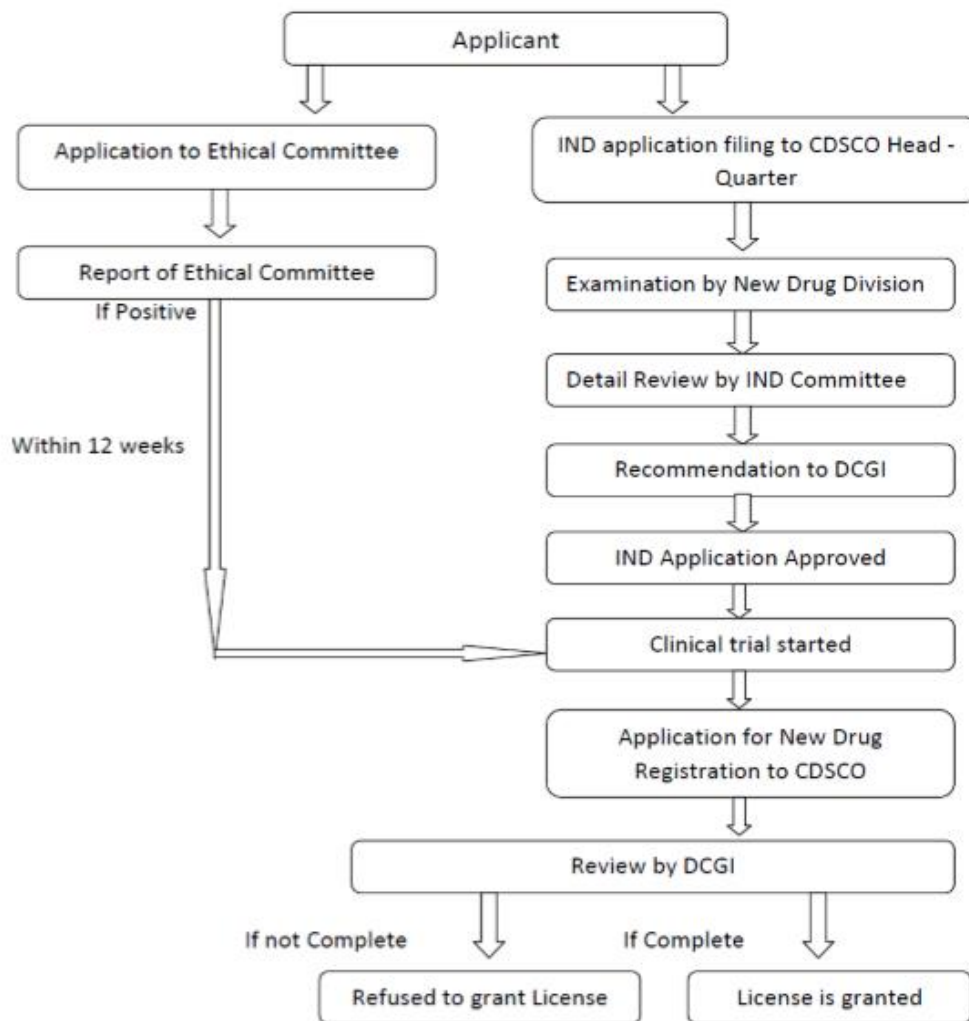


Figure 5. Drug approval Process in India

5. Difference between EU & India

Table 1 Regulation difference between EU & India

Requirements	Europe	India
AGENCY	Multiple agencies <ul style="list-style-type: none"> • EMEA • CHMP • National health agency 	One agency - DCGI
REGISTRATION PROCESS	Multiple process of registration <ul style="list-style-type: none"> • Centralized procedure • Decentralized procedure • Mutual recognition procedure • National procedure 	One procedure only
TSE/BSE study data	Required	Required
Post Approval Changes	3 types- <ul style="list-style-type: none"> • Type IA variation • Type IB variation • Type II variation 	2 types- <ul style="list-style-type: none"> • Major quality changes • Minor quality changes

Table 2 Difference between Administrative Requirements of EU & India**Administrative Requirements**

Requirements	Europe	India
APPLICATION	MAA	MAA
NO. OF COPIES	One copy	One copy
APPROVAL TIME	~ 12 months	12 – 18 months
PRESENTATION	eCTD	Paper

6. Conclusion

Currently the Drug Approval Process in Europe & India is the most important and demanding in the world. The main purpose of regulating all the medicinal products by regulatory agencies is to safeguard public health. Regulatory agencies work is to make sure that the pharmaceutical companies comply with all the regulations and standards, so that the patient's well-being is protected.

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Conflict of interest

The authors declare that there is no conflict of interest.

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