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A COMPARITIVE STUDY OF THE DRUG APPROVAL PROCESS IN USA, INDIA, JAPAN AND EUROPE

Akhilesh Chandra[1]* and Bhumika Kumar[1]

[1]Department of Pharmaceutics, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar, Sec-3, New Delhi 110017, India.

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***Corresponding Author**
Akhilesh Chandra
Department of Pharmaceutics, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar, Sec-3, New Delh 110017, India

ABSTRACT

Safety and efficacy of a drug product for use in humans is essential before the drug product can be approved for import or manufacturing a new drug. For this every country has its regulatory authority that bears the responsibility of evaluating whether the research data of new drug/product supports the safety and efficacy to serve public health. Regulatory affair department of a company plays a vital role of working in accordance to the rules, regulations and guidelines established by the regulating agencies of different countries. This article aims to compare different aspects of drug approval process in USA, Europe, India and Japan.

KEYWORD: FDA, EMA, PMDA, CDSCO, MAA, NDA, INDA, ANDA.

INTRODUCTION

Regulatory affair department is a bridge between the pharmaceutical companies and government agencies which works towards protection of public health by controlling the safety and efficacy of a product. It is actively involved in each and every stage of development of a new product, from its discovery to the post marketing activities.

Different country has its different regulatory agencies because single approach is almost a difficult task and not effective in providing safety to public health. So regulatory affairs department in a company has adequate knowledge of regulatory guidelines of each country to ensure their company comply with all of the regulations and laws concerning their business. Regulatory Affairs is involved in the development and marketing of new medicinal products by integrating regulatory principles and by preparing and submitting the relevant regulatory

dossiers to health authorities. So filling process for approval of new and abbreviated drug in USA, Europe, India and Japan is summarised in this article.

USA

The food and drug administration (FDA) is the single agency which regulates safety and efficacy in US food supply, prescription drug & devices to human health core. It also covers electronic product (emit radiation), cosmetic, animal product and it also regulates the manufacturing of tobacco products. Pharmaceutical companies have to follow difficult and stringent rules & regulations for bringing the product to the market for public use.

FDA is centrally headed by a commissioner who is appointed by the president with the consent of the senate. It's the scientific law enforcement agency which provides law for providing safe guard to public health. FDCA (food drug and cosmetic act) of 1938 regulates food, drug cosmetic and medical device for both human and animal use, it is turn establishes FDA.

For pharmaceutical and biological drug evaluation

- Centre for drug evaluation and research (CDER)
- Centre for biological evaluation and research (CBER)

NEW drug neither safe nor effective until proper testing is done & FDA approval is obtained.

Preclinical investigation: In Preclinical studies information is gathered by doing in vitro and in vivo tests to find out Pharmacology, toxicology, carcinogenicity of a substance which gives sufficient knowledge about the substance whether it is useful to make it as a new drug for medicinal use or not or it will give safety in humans before it is tested on humans.

IND (Investigational new drug application): Information from the preclinical study about the substance and also manufacturing area & lab control document is compiled to form a protocol. This protocol with the result of the test is organised with IND application which is submitted or filled to FDA (CDER). IND application is filed to FDA for starting clinical trials on human beings. IND phase is a clinical phase from where safety and efficacy data about the potential drug compound is gathered for evidence whether it is of human use or not. Company or sponsors submit all the study about the substance which provides valid evidence for safety and efficacy with IND application to FDA (CDER).

INDA content

Table of content, introductory statement / investigational plan, comprehensive investigational protocol, actual compound and proposed chemistry, manufacturing and control, any pharmacological and toxicological information, any previous human experience and other necessary required documents and studies listed in guidelines for INDA by FDA.

Before actual clinical investigation commencement, the developed protocol is revised by IRB (Institutional review board). It is a committee designated by an institute who ensure that the rights of human tests are protected and scientific and medical standards are maintained. CDER give complete review and evaluate the data and documents given by the sponsor with INDA. If they found it acceptable they approve the substance for further studies that is clinical trials. Clinical trial is composed of three phases:

Phase **(I)** Determines toxicology, metabolism and pharmacological action in 100 subjects. Phase **(II)** done on several hundred subject afflicted with the disease or condition being studied. phase **(III)** Long term trial on several thousand subjects for several months & years for establishing final formulation, indication, labelling, marketing claim and product stability, Packaging and storage condition which meets the safety and efficacy standards which FDA requires for approval in US marketplace. For getting the product into the US market the process begins with NDA submission.

New drug application (NDA): If the drug substance proves its safety and efficacy in clinical trial phases and does not pose any risk to the patient, manufacturers files NDA. It is an application which requests the FDA to approve and permit the manufacturing and selling of the drug in US if they found public benefit and safety by evaluating the clinical trial data and all study of new drug product. Sponsor submit NDA with all information data from clinical trial phase in a appropriate manner in form CTD and eCTD (electronic common technical data) according to guideline given by FDA.

CTD (common technical data) is a standard format of document submitted with NDA. It is submitted on papers or through electronic way (eCTD in USA and CTD in India).

CTD is organised into five modules: (Overview).

MODULE 1

Administration and prescribing information specific for USA.

MODULE 2: CTD overview and summary

- Introduction
- Quality overall summary
- Overview of non clinical studies
- Non clinical summary
- Clinical summary
- Clinical overview

MODULE 3: Quality summary

- Drug substance
- Information of starting and raw material
- MFG process, characterisation and quality of drug substance etc.

MODULE 4: Non clinical study report

• Report on study, pharmacology, Pharmacodynamics, pharmacokinetics, toxicology, toxicity of adjuvant etc.

MODULE 5: Clinical report study

- Phase I study
- Phase II study
- Phase III study
- BA/BE study

Process after filing NDA

1. Review by CDER in the field of medical, biopharmaceutical, pharmacology, chemistry and microbiology of drug formulation

2. Evaluation of the data

3. Meeting with Advisory committee and request for their review

4.Sponsor and CDER meeting is also held

5. Review acceptable or not. If yes then site where clinical trial are performed and new drug manufacturing site is inspected and labelling acceptance is considered.

6. If no then FDA notifies sponsor for either giving additional information or request for revision which is again reviewed by CDER.

7. CDER NDA approved – permit to manufacture the new drug formulation for US market (phase IV- marketing phase).

Abbreviated new drug application (ANDA)

When patent of a drug expires in US marketplace and company wishes to market the generic they have to file ANDA which give all information about the biopharmaceutical and pharmaceutical equivalence study data of generic with the standard or previously approved active pharmaceutical ingredient in same market holding drug listed in orange book. Orange book contains list of all the drugs approved by FDA as safe and effective for public health. This approved drug is used as a standard for approving their generic formulation by giving evidence that the generic drug is bioequivalent and pharmaceutically equivalent to the standard drug.

Process of ANDA is same like NDA but only difference is that field in which CDER and OGD (office of generic drug) give review and evaluate data of bioequivalence study, chemistry or microbiological review, plant inspection and labelling review. If both departments found the generic equivalent in all aspect with the standard according to the guidelines, then the generic is approved for US market.

INDIA

Licensing authority of India is Drug controller general of India (DCGI) who approves and permits a new drug product manufacturing and marketing in India. Central drug standard control organisation (CDSCO) is a government agency that evaluates the applicant new drug product for its safety and efficacy and gives the review report to DCGI. Drugs and Cosmetics Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacturing of a new drug for Indian market. Schedule Y of Drug and Cosmetic rule 1940 and rule 1945 provide guidelines and required data for clinical trials for its approval. CTD (common technical data) is the only format for submitting information to CDSCO. Applicant submits one hardcopy and three soft copies of dossier. CTD is applicable to all type of approvals. API previously

Approved is not applicable for new finished product, company have to take permission from CDSCO by providing bioequivalence study data of safety and efficacy of new product. Drug discovered in India have to go through all trial phase (section 2.1(a) schedule Y). Drug which is approved in other country there is provision in Act 1940 and 1945 section 122A that if regulatory authority of India found interest for public health it may waive certain trial for granting permission for importing new drug but applicant has to submit the entire document related to trial done of drug in the previously approved country.

CTD is a standard format of document submitted with marketing authorisation Application. It is submitted on paper (eCTD in USA).

Process for approval new drug: Approval process contains two phase, first phase comprising of clinical trial permission (INDA) and second phase for market authorisation (NDA).

FIRST PHASE

1. Application for INVESTIGATIONAL NEW DRUG is submitted along with chemistry, manufacturing, control and animal studies to CDSCO headed by DCGI
2. One copy is also submitted to ethical committee
3. Examination and evaluation of new drug.
4. IND committee review and reports to DCGI
5. DCGI takes decision in accordance to IND committee report and ethical committee report.
6. INDA approved by DCGI and give permission for clinical trial studies

SECOND PHASE

7. Three phase clinical trial done
8. Filing of NDA for registration with clinical and non clinical data(CTD)
9. Data Reviewed and evaluated by DCGI and CDSCO
10. If complete, then licence granted for market authorisation, if not then deficiency letter is send to the company.

For registration: Form 44 and fees of 50000 INR.

Process of approval of drug not approved in India but approved in other country

- Form 44 with fees 50000 INR
- All the data related to the drug for approval should be submitted which contain pre-clinical and post clinical data of the country in which the drug was previously approved.
- The data is reviewed by DCGI and appropriate decision is taken whether they have to do all the trials or waive some trials and give permission for conducting phase III clinical trial.

Generic drug approval: This application is quite different from the new drug application. In this application CDSCO and DCGI may allow the applicant and regulatory authorities to rely

on some part of the safety and/or efficacy data for a previously approved drug. However, additional nonclinical and/or clinical data is required to substantiate the new claims of the approved drug. The additional data needed for establishing the safety and efficacy of new generic drug is determined according to the new claim. If the drug is already approved by various agencies and is being marketed in major countries for the proposed new claim. If the generic drug proves its bioequivalence and pharmaceutical equivalence with approved drug and confer for no change in metabolism due to ethnic difference. Requirements of Animal Toxicological & clinical data may be abbreviated or relaxed if the proposed new claim is for serious life threatening disease or disease of special relevance. CDSCO will examine the adequacy of such applications for the purpose of granting approval for manufacture/import of such new drugs. Wherever required the matter may also be examined in consultation with experts/expert committees.

JAPAN

Regulatory authority of Japan is PMDA (pharmaceuticals and medical device agency). PMDA is the agency that reviews submission of applications for drug approval, foreign manufacturer accreditation (FMA), drug master file (DMF) registration, etc. set up by ministry of health labour and welfare (MHLW). The PMDA also provides guidance regarding clinical trials and data required for approval applications etc. Using the face-to face consulting services (paid) can aid the application process. Four phases of consultation are: before INDA, at the end of phase II study, before NDA and consultation on individual protocols.

Drug approval process goes through IND and NDA procedure in Japan. For approving new or generic drug in Japan all data and document is submitted as MASTER FILE, with specified form which allow Japanese and foreign manufacturer of drug substance for registering the data for approval in accordance to the procedure described in Enforcement regulation for pharmaceutical affair law.

Foreign manufacturer have to obtain FMA (foreign manufacturer accreditation) before master file filing because this application wants accreditation number, category and date of FMA issued. And for foreign manufacturer they have to undertake a person of Japan addressed who has duty for master file registration. (In-country care taker of drug substance) (Article 72).

Japanese applicant should hold a MAH (Market authorisation holder) licence and foreign applicant contains FMA. Then master file is sent to PMDA for further examination. Japan work under ICH GCP guideline for clinical trial since 1997.

Process for approval

1.First applicant has to submit INDA to ministry of health, labour and welfare.

2.PMDA review and report and sent to IRB(institutional regulation board)

3.IRB review and approval

4.Study initiate

5.MF registration application with data

6.Data must be in the form of CTD

7.Team based review and investigation

8.Reviewer and expert(external) discussion on main issue

9.Summary of main issue

10. Presentation and discussion with applicant on main issue chaired by director on charge of review.

11. Expert and reviewer discussion

12. Review report and result to ministry of health, labour and welfare (it also consult with pharmaceutical affair and food sanitation council)

13. Approval

Publication of Information

As for a new drug, an Assessment Report is published right after the approval and the outline of application document (Module 1 (partially) and 2 of CTD) is published in three months after the approval.

Process of approval for generic drug

Main data required for the generic drug approval

- Manufacturing method, standard and test method for evaluating.
- Stability data for accelerated study
- Bioequivalence study.

Active ingredient should be registered then generic manufacturer provide above data with API master file number. PMDA give review report to MHLW who permit the applicant of generic drug.

Fees: Drug containing new ingredient, biotechnology based existing drug (excluding an orphan drug):31,068,900 yen.

Drug containing new ingredient, biotechnology based existing drug (orphan drug):23,847,800 yen.

Drug with a new indication, drug with similar formulation (excluding an orphan drug):14,230,600 yen.

Drug with a new indication, drug with similar formulation (orphan drug):10,957,300 yen.

EUROPE

For placing medicinal product or drug in the European market (EEA-Europe Economic Area) manufacturers have to take market permission from member state authority of its own territory (national authorisation) or when authorisation has been granted with regulation (EC) NO-726/2004 for entire union (union authorisation).

(Market authorisation holder must be establish within EEA)

Market authorisation is composed of

- Division of granting the market authorisation issued by relevant authority
- Technical dossier submitted with relevant data by submitting application in accordance with article 8(3) to 11 of directive 2001/83/EC & annexe I, Article 6(2) & 31(2) of regulation (EC) No 726/2004 or article 7 of regulation (EC) No 394/2007.

EEA: Norway, Iceland and Liechtenstein form EEA with 28 member state of EU (July 2013). EEA adopted an agreement in complete union acquis on medicinal product which makes a union procedure for approval. If Union approve any drug, Norway Iceland and Liechtenstein take corresponding decision on the basis of relevant act (Decision No 74/1999 of EEA joint committee).

National authorisation: It is the authorisation of drug in single member state. But if applicant wants permission for another member state then it has to submit separate application to another member state with data approved in previously member state by going through mutual recognition procedure. And if applicant is not registered in union then it proceeds for approval by decentralised process.

Union authorisation: union will grant the permission for medicinal product by using centralised procedure (Annexe to regulation EC No 726/2004).

There are two stage processes in Europe for approval, first is clinical trial stage and second one is market authorisation stage. Clinical trial approved by member state but market authorisation is approved by both member and centralized level.

Procedure for approval: For Market authorisation of new medicinal product in Europe companies use three approval procedures

1. Centralised: This is the procedure by which applicant can approve its product for marketing in whole EU. This will take around 210 days and European medicines agency (EMA) evaluate the product and send it to the European commission for final approval after consulting with committee for medicinal product. Centralised authorisation is mandatory for some type of drug like genetically engineered drug, orphan drugs and drug used for HIV/cancer, Neuro disorders, autoimmune, diabetes etc. (Article 14(8) of regulation (EC) No 726/2004 and article 22 of directive 2001/83/EC).

2. Decentralised: This procedure is used for that drug which does not come under the centralised essential drugs. Mainly companies use this procedure for approving the product (that have not yet been approved in any member state) in more than one EU member state by submitting the application to each EU member state and giving reference member state (RMS) number with each application to concerned member state (CMS), which undertake that applicant submitting the dossier file is identical to all the member state. RMS and CMS comments are reviewed than market authorisation will be granted. Time 210 days.

3. Mutual recognition procedure: This procedure is used by those applicants whose drug is approved previously in one member state by giving RMS number to one or more CMS where they want approval. Data should be identical. Time 390 days.

Table: Different drug filing procedure in Europe

CENTRALISED	DECENTRALISED	MUTUAL RECOGNITION
MAA	Application to RMS and CMS	Application to RMS and CMS
Assessment report (co-rappoteur) EMA	RMS and CMS validate the data	RMS send review report to CMS
CHMP review and comment	RMS and CMS review and comment	CMS validate the report and data
Applicant answer the question	RMS send all report to CMS	CMS approval

Final draft to EMS CHMP	CMS validate the report	Market authorisation to each CMS
CHMP opinion	Approval in RMS and all CMS	
Approved in Union		

CHMP*: Committee for medicinal product for human use.

CONCLUSION

The major purpose of making rules and regulations stringent for medicinal products is to provide safety to public health. It is the responsibility of these regulatory authorities to ensure that the pharmaceutical companies abide to the rules and regulations to safeguard public health. The drug regulatory affair authorities play a very crucial role from the development of a drug to its manufacturing. Thus, these regulatory bodies are very essential in providing safety to a consumer.

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