DRUG APPROVAL PROCESS: A CONTRASTIVE APPROACH

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REVIEW ARTICLE

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ABSTRACT:

The drug approval process is the vehicle through which drug sponsors formally approve a new pharmaceutical for sale and marketing. The goals of the approval process are to provide enough information about the drug safety and efficacy in human beings. 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. The approval process starts with preclinical testing. For drugs that appear safe, an investigational new drug application (IND) is filed. If approved, clinical trials begin with phase 1 study 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 to the authority. A New Drug Application (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.

Keywords: Drug approval process, NDA, IND, Clinical trial, Marketing authorization.

Introduction

Drug approval process is the regulatory process by which any person /organization /sponsor/innovator gets their drugs approved for launch in market. It is an obligatory step before the launch of a drug into the market. Today, the regulatory requirements for approval of drug in various countries of the world are quite different. Every country has its own regulatory authority which is responsible to enforce the rules and regulation and issues the guidelines to regulate the marketing of the drugs. In general, in every country the drug approval process comprises firstly; the submission of application to conduct clinical trials which is filed by sponsor when non-clinical studies data of a drug shows an acceptable efficacy and safety into animals. Secondly; application to marketing authorization of drug is submitted when the clinical studies of the drug are complete and clinical trial data certifies the efficacy, safety and optimized dose of the drug in human beings. The sponsor files an application to the competent authority of the concerned country for approval of drug for marketing. The competent authority reviews the application, if they find that drug is safe and effective; competent authority gives marketing approval (1, 2).

Drug approval process in USA: Crack down on safety first/safe use

The United States historically has been the world largest market for pharmaceuticals. The Food and Drug Administration is the agency of the United States which is responsible for drug approval process, protecting and promoting public health care. The primary aim of FDA was to create a united standard for product review among national regulatory authorities. The following regulations apply to the IND application process (3-5):(Table 1)

Table 1: Regulations applying to the IND application process

Code of Federal regulation	Type of applications
21CFR Part 312	Investigational New Drug Application
21CFR Part 314	IND and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling

Drug approval process in US comprises of the following steps in detail with an aim to protect and promote the health of Americans (6,7):

- Application to conduct clinical trial (IND)
- Marketing Authorisation
- Post Approval Studies

Application to conduct Clinical trial (IND)

The approval process of new drug is started when sponsor submit the application for the conduct of clinical trial which is called as Investigational New Drug Application. After the submission, application is reviewed by competent authority Center for Drug Evaluation and Research (CDER). Once the fileability is established, an IND number is assigned along with the date of receipt and initiates the 30 days review clock. If the review team determines that the deficiency in the IND is not of serious nature, a deficiency letter is sent to the sponsor. The IND studies generally may proceed if the sponsor is not informed of the contrary within 30 days of receipt (8).

Marketing Authorisation

When all the clinical studies are over and the result of clinical studies shows that drug has more beneficial effects as compared to the adverse effects, the applicant looking for approval of drug from FDA to launch the drug in marketfiles NDA. The process of marketing authorisation of drug includes firstly, application for marketing authorisation of drug and secondly, reviews of application by FDA and approval or disapproval of drug.

Application for marketing authorisation of drugs:

In USA following four types of application are submitted for the approval of drug for marketing authorisation depending on the type and nature of the drugs (9):

- New Drug Application (NDA)
- Biologics License Application (BLA)
- Abbreviated New Drug Application (ANDA)
- Supplemental New Drug Application (sNDA)

Review of application by FDA

Upon receipt, the central document room of CDER of FDA stamps the NDA with a receipt date. This date is very important because by federal law the agency must forward to the applicant an action within 180 days that indicates whether the NDA is approvable or not. The FDA has 60 days, from the receipt of the application, to determine whether application is adequate for review. If the application is deemed inadequate, FDA can refuse to file it and the sponsor can resubmit it later otherwise no. Toward the end of the review process, FDA and the sponsor negotiate the drug safety, efficacy and final package label. Each element of the label requires FDA approval. Once all the review is

complete, the division director evaluates the review and makes decision. The review clock ends once FDA makes its decision and issues a letter to the sponsor. The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored (10, 11).

Drug approval process in Europe

The European system for the authorisation of medicinal products for human and animal use was introduced in January 1995 with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union. The European system offers several routes for the authorisation of medicinal products (12-16).

The drug approval process in European Union comprises the following steps:

- **Clinical trials authorization**
- **Clinical studies**
- **Marketing authorisation of drug**
- **Clinical trials authorisation**

Any sponsorseeking approval of a new drug in European Union member states should take clinical trials authorisation to conduct the clinical studies to assess the safety and efficacy of drug. Clinical trial authorisation procedure compriseof the two steps; firstly, application to conduct clinical trial and secondly, review of application by the competent authority of member state. When sponsor submit an application to the competent authority, the sponsor must obtain a unique Eudra Clinical Trial (Eudra CT) number from the EMEA Eudra CT database. This number identifies the protocol of the clinical trial.

On the receipt of the application, the competent authority of the member state starts to validate the application and an acknowledgement letter is sent to the person submitting the application. If the application is valid then the assessment period will begin. This starts from the date of receipt of a valid application. If the application is not valid the person making the application is informed about the deficiencies.

The MHRA website mentions that the initial assessment will be performed within 30 days. There are two possible outcomes of the approval process; firstly, acceptance and secondly, grounds for non-acceptance. If there are grounds for non-acceptance, the sponsor has at least 14 days (at least 30 days for gene therapy, somatic cell therapy or product containing genetically modified organisms) to submit an amended request for authorisation.

- **Clinical studies**

Clinical studies of any medicine is done into 4 phase. It provides the safety and efficacy data of the medicine.

- **Marketing authorisation of the drug**

Any person desiring to market a drug within the European Union should take marketing authorisation of the drug. This process ofcaptivating marketing authorisation can be understood in two steps as (17):

- Marketing authorisation application (MAA).
- Procedure of marketing authorisation

Marketing authorisation application (MAA): its contents and formats

The application files to approve the drug for interstates commerce in the European Union is called MAA. The MAA should be file in the CTD format which contains the five modules. The content of the application depends up on the nature and type of the drug for which MMA file, i.e.,

- For the Drug containing a new molecular entity, the application contains all five modules ,or for new combination of

already approved ingredients, the application may or may not contain the non-clinical and clinical studies reports depending on the either change alter the therapeutically index of the drug.

- For a Generic Drug, the application does not contain the module-4 and contain only comparative bioavailability and bioequivalence studies in module-5.

Procedure of marketing authorisation

When seeking approval to market a new drug in Europe, there are several options: a national authorization procedure, a decentralized procedure, a mutual recognition procedure, or a centralized procedure (17).

National authorization procedure

Each country within the EU has its own procedure for authorizing a marketing application for a new drug. A sponsor can consult the website of the regulatory agency in each country in which it is interested in obtaining marketing approval to obtain details of the approval process. A sponsor can also seek approval of several EU countries simultaneously using the decentralized or mutual recognition procedure.

Mutual recognition procedure (MRP)

The MRP has been in place in the EU since 1995. The objective of this procedure is to obtain marketing authorizations in one or several Member States, when the medicinal product has already been granted authorization by at least one country in the European Community (18).

With the mutual recognition procedure, a product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country. Thus, in this case, the applicant requests one or more concerned member state (CMS) to mutually recognize the authorization granted by the Reference member state (RMS). (Figure 1)

If the marketing authorization in the RMS is based on an old dossier format, it is an obligation to reformat the dossiers before starting the MRP. The marketing authorization holder should submit an application to the competent authorities of the RMS and each of the CMS(s). Within 90 days of receipt of a valid application by the RMS, the RMS provides the Assessment Report, or if necessary, updates any existing one and sends it together with other documents to the CMS and to the applicant. Within 90 days, the CMS recognize the decision of the RMS. Thirty days after the close of the procedure; the competent authorities of the CMS adopt a decision and grant marketing authorization. Therefore, at the end of the MRP with a positive agreement, a national marketing authorization will be issued in each of the CMS.

Centralized procedure

The Centralised procedure, which came into operation in 1995, allows applicants to obtain a marketing authorisation that is valid throughout the EU (17, 19).

Products that are eligible for review under the centralized procedure must meet the following criteria:

- Biologic drugs developed by recombinant technology and monoclonal antibody methods
- Medicinal products containing new active substances (AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases), Orphan medicinal products

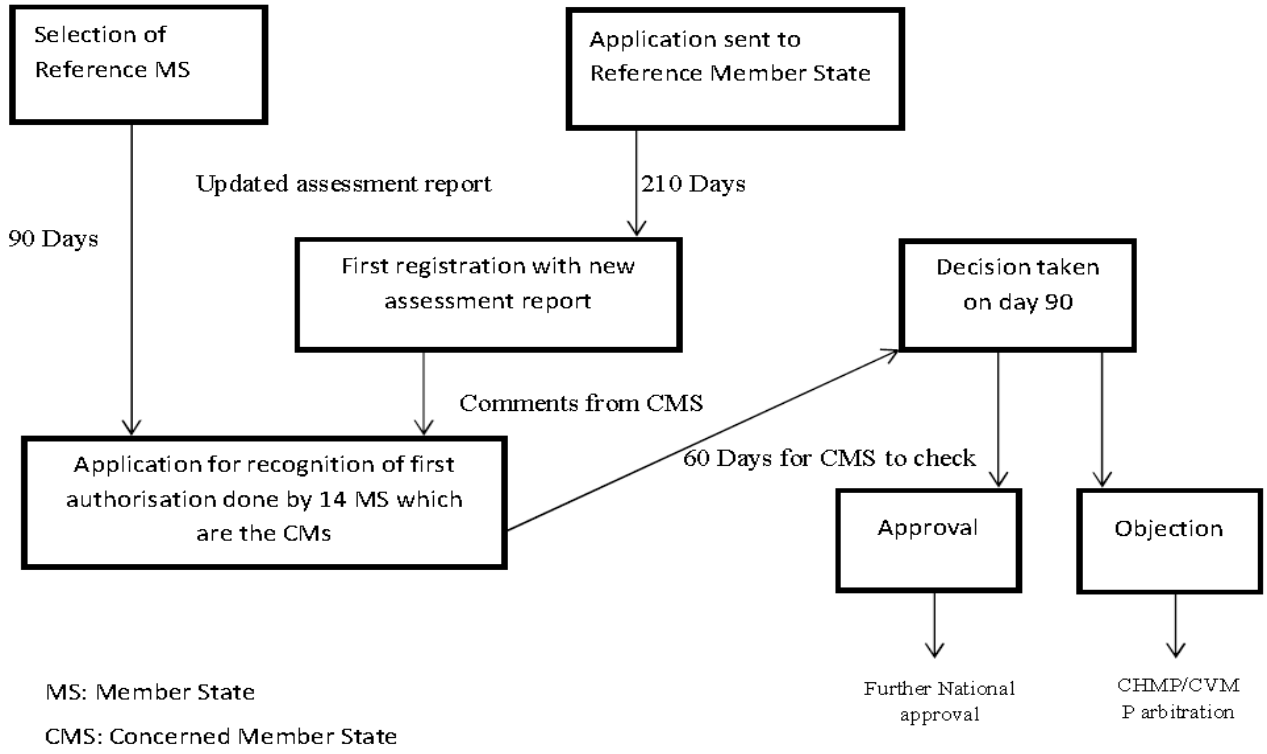

Figure 1: Mutual recognition procedure (MRP)

When a company wishes to launch medicinal product in market is eligible for the centralised procedure, it sends an application directly to the European Medicines Agency, to be assessed by the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Medicinal Products for Veterinary Use (CVMP) for veterinary product. The procedure results in a Commission decision, which is valid in all EU Member States. After that full copies of the marketing authorisation application file are sent to a rapporteur and a co-rapporteur designated by the competent EMA scientific committee. They co-ordinate the EMA's assessment of the medicinal product and prepare draft reports. Once the draft reports are prepared, they are sent to the CHMP or CVMP, whose comments or objections are communicated to the applicant. The rapporteur and co-rapporteur then assess the applicant's replies, submit them for discussion to the CHMP or CVMP and, taking into account the conclusions of this debate, prepare a final assessment report. Once the evaluation is completed, the CHMP gives a favorable or unfavorable opinion. When the opinion is favorable, it shall include the draft summary of the product's characteristics, the package leaflet and the texts proposed for the various packaging materials. The time limit for the evaluation procedure is 210 days.(Table 2) The EMA then has fifteen days to forward its opinion to the Commission. This is the start of the second phase of the procedure: the decision-making process. The Agency sends to the Commission its opinion and assessment report. During the decision-making process, the Commission services verify that the marketing authorisation complies with Union law. The Commission has fifteen days to prepare a draft decision. The medicinal product is assigned a Community registration number, which will be placed on its packaging if the marketing authorisation is granted. During this period, various Commission

directorates-general are consulted on the draft marketing authorisation decision. The draft decision is then sent to the Standing Committee on Medicinal Products for Human Use, or the Standing Committee on Veterinary Medicinal Products (Member States have one representative each in both of these committees) for their opinions. They give their opinion, if opinion is favorable, the draft decision is adopted the empowerment procedure. The Commission's Secretariat-General then notifies the Commission Decision to the marketing authorisation holder. The decision is then published in the Community register. Marketing authorisation is valid for five years. Applications for renewal must be made to the EMEA at least six months before this five-year period expires. (Figure 2)

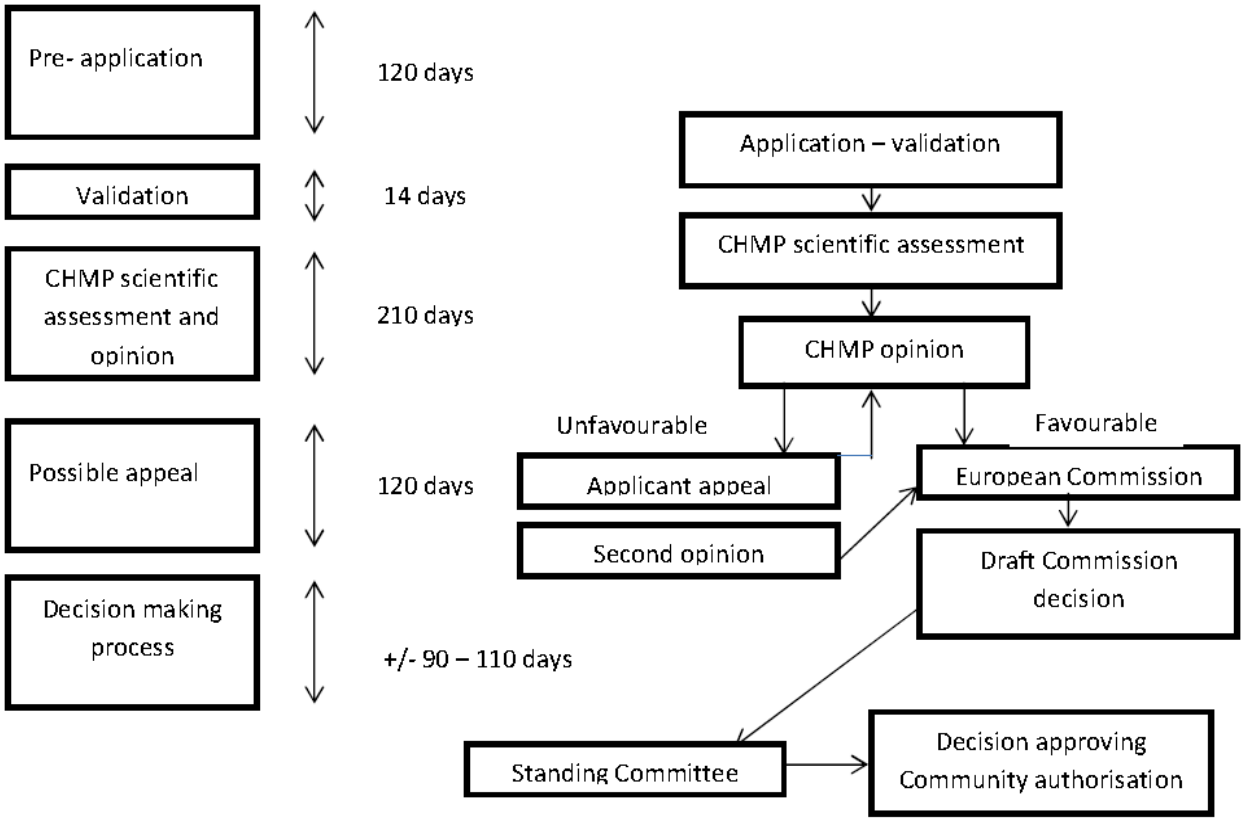

Figure 2 Centralized procedure

Decentralized procedure

For products that fall outside the scope of the European Medicines Agency with regard to centralized procedures, a sponsor can submit under the decentralized procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country (20).

The objective of this procedure is to obtain marketing authorizations in several member states, when no marketing authorization has been granted in the European community. The applicant should send an application to the competent authorities of each of the Member States, where there is intent to obtain a marketing authorization. The applicant may designate a country to act as the Reference Member State (RMS). Selection of the RMS depends on many considerations including workload, previous experience, interests, and acceptance of the dossier by the RMS. The RMS will start the procedure after the

application is determined to be complete by both the RMS and all the CMS. The RMS forwards a preliminary Assessment Report on the dossier to the CMS. The CMS is asked to give comments on the proposed national prescription status and to inform the RMS. On day 105, the RMS will forward all comments to the applicant and stops the clock if necessary, until the applicant prepares a response document. The RMS prepares a Draft Assessment Report on day 120 and may close the procedure if a consensus has been reached between the CMS and the RMS. Otherwise; the CMS has 90 more days to approve the Draft Assessment Report, and other documents. Competent authorities of the RMS and the CMS adopt a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents. At the end of the Decentralized Procedure with a positive agreement, a national marketing authorization will be issued in the RMS and each of the CMS (17,18).

Drug approval process in India

In India, drug manufacturing, quality and marketing is regulated in accordance with the Drugs and Cosmetics Act of 1940 and Rules 1945. The Drugs Controller General of India (DCGI), who heads the Central Drugs Standards Control Organisation (CDSCO), assumes responsibility for the amendments to the Acts and Rules. Drugs and Cosmetics Act of 1940 and Rules 1945 hasSchedule Y; which, specifies guidelines for clinical trial, import and manufacture of new drugs. The central regulatory authority undertakes approval of new drugs, clinical trials, standardsetting, and control over imported drugs. Like general drug approval process, new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug registration. In India, two different provisions are present; One for the new drug substances discovered in India, these clinical studies are called Domestic clinical studies and other for the drug discovered in country other India, these clinical studies are called Global clinical trials (21-24).

The clinical studies for the new drugs which are discovered in India are stated from phaseI. For permission to conduct clinical trials are applied in Form 44, and the same form is used for new drug approval.

For the drugs that are discovered outside India, the Drug Controller General of India has continued the two-track system for regulatory approval of clinical trials which are:

Category A: Drugs that have already gained approval by the regulatory bodies in the US, Germany, UK, Switzerland, Australia, Japan, South Africa, Europe, Canada. For this type of drugs only a phase III clinical studies are required.

Category B: Application for trials that are not already approved by another recognised regulatory agency. These types of application may be submitted to any phase of clinical trials.

On the receiving the application for clinical Trial, the head quarter of CDSCO propel it to new drug division where it is received by IND committee. After complete review the IND committee sends their recommendation to the DCGI. If the report of the IND committee is favorable, the DCGI approves the application.

In India, time for regulatory approval of CTA/IND application is about 16- 18 month. Beside the approval from HA, international applicant also needslicence to import the clinical trial sample and permission from Directorate General of Foreign Trade to export blood sample for analysis to a central laboratory. The Ethical Committee (EC) approval can take from 1-3 months. However, EC review the application only after the HA permission.

New drug registration process in India

After successful accomplishment of the clinical trials, applicant applies registration of new drug in Form 44. All submissions require basic dosage and indication information, test specification of active and inactive ingredient, listing of any applicant's patents, and raw material manufacture. This application requires full preclinical and clinical testing information. The application should be prepared in CTD format. After receiving the application, the DCGI of India starts the review of the application. When all information submitted with the application proves that the drug is safe and effective in human being, a licence is issued o applicant for marketing it in India. Time taken in evaluation of marketing authorisation application is about 8-12 week (Table 2) (24,25).

Table 2: Comparison of Drug Approval Process

Name of country	Marketing Authorisation Application Fee	Time for regulatory approval of IND	Time taken in evaluation of MAA
USA	$217787	30 Days	180 Days
European Countries	PS254100	35 Days	210 Days
India	50000 INR	16-18 Weeks	8-12 Weeks

MAA-Marketing Authorization Application, IND-Investigational New Drug

Conclusion

From the above review it can be concluded that, developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. The new drug approval process consists of two stages (phases) - the first phase is for clinical trials and second phase is for marketing authorization of drug. Firstly, non-clinical studies of drug are completed to ensure safety and efficacy. The next step is the submission of application for conduction of clinical trials to competent authority of respected country. In next step, clinical trials are carried out in four phases i.e. phase 1 – phase 4 study. These studies are carried out for the assurance of safety, efficacy and for optimization of dose of drug in human being. Then application for marketing of drug is carried out by competent authorities. The competent authority review the application and approve the drug for marketing purpose, only if that drug found to be safe and effective with desired effect as compare to adverse effect.

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