EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 9
408-416
Year: 2022

AN OVERVIEW ON GENERIC DRUG APPROVAL PROCESS IN US AND EUROPE

*[1]Abdul Mannan, [1]Nahl Imtiaz Mohammed, [1]Rahila Fatima, [1]Shafiya Begum and [1]Faroza Khatoon

*Corresponding Author: Abdul Mannan

Article Received on 19/07/2022 Article Revised on 08/08/2022 Article Accepted on 29/08/2022

ABSTRACT
Generic drugs are identical to branded drugs in terms of dosage form, safety, strength, route of administration, performance, and intended use. Developing a new drug requires a great amount of research work in chemical, manufacturing, control, pre-clinical, and clinical process. Every country has its own regulatory authority which is responsible to enforce rules & regulations and issue guidelines to regulate the marketing of drugs. For a generic drug to be marketed the company must submit Abbreviated New Drug Applications Approval. This article focuses on the drug approval process in different countries like US, and Europe. Drug approval Standards in US is considered most demanding and truly reliable in the world whereas the approval process of Europe is typical and contains more data to be summarized for dossier submissions.

KEYWORDS: ANDA, Federal regulations, Hatch Waxman act, eCTD, EMA, Marketing authorization.

INTRODUCTION

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is performs in the same manner as the innovator drug. One-way applicants demonstrate that a generic product performs in the same way as the innovator drug is to measure the time it takes the generic drug to reach the bloodstream in healthy volunteers. This demonstration of “bioequivalence” gives the rate of absorption, or bioavailability, of the generic drug, which can then be compared to that of the innovator drug. To be approved by FDA, the generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.[1]

US FOOD AND DRUG ADMINISTRATION (USFDA)

The USFDA is a scientific, regulatory and public health agency that jurisdiction encompasses on most food products (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, medicinal devices, radiation-emitting products for consumer, medical occupational use, cosmetics and animal feed. The Office of the Commissioner heads the organization under which there are four departments overooking management, health, and science, international activities and regulatory affairs. They have various centers for regulation of medicinal products, medical devices, food, veterinary products and also toxicological research. The organizational structure of the USFDA is shown in Figure 1. The FDA is also responsible for advancing the public health by helping to spend innovations that make medicines and food more effective, safer, more affordable and helping the public to get proper, scientific information about the food and medicines to improve their health.[2]

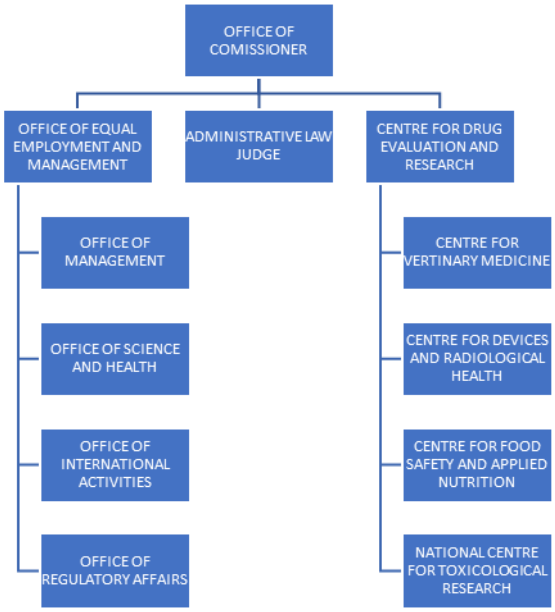

Fig 01: Organization chart of USFDA.

The Documents or the application submitted to the FDA for the approval of a generic drug product is known as an Abbreviated New Drug Application or ANDA. It contains all the data for FDA review and approval.

AN OVERVIEW ON GENERIC APPROVAL PROCESS BY USFDA

Once the ANDA is approved the manufacturer can market the safe, effective, and less expensive generic version. Generic drug applications are referred to as "abbreviated" because they are not required to submit any clinical and animal studies to prove their safety and efficacy. The generic drugs are scientifically proven to be having the same properties to that of the innovator drug. To demonstrate that a generic drug is similar to an innovator drug is to measure the bioavailability of the drug in the systemic circulation of healthy volunteers. Bioavailability, the rate of absorption of the generic drug is evaluated by conducting a 'Bioequivalence' study and is compared to the branded drug. To be approved by FDA, the amount of active ingredients in the circulatory system of the patient should be the same for both the generic and the innovator drug. Enactment of the Drug Price Competition and Patent Restoration Act of 1984, better known as "The Hatch- Waxman Act" is the major force for generic market development in the US. It has created opportunities for developing and marketing generics or better called an abbreviated new drug application for 180 days. Final approval of ANDA by the FDA takes minimum18 months. Under ANDAs a pharmaceutical manufacturer can develop and market low price generic versions of previously approved innovator drugs, thus providing the same product to a patient at a pregnable price with safety and efficacy all approved products, both innovator, and generics, are enlisted in FDA's orange book.[2]

Types of certifications

The "Drug Price Competition and Patent Term Restoration Act of 1984", also known as the Hatch-Waxman Amendments, established bioequivalence as the basis for approving generic copies of drug products. These Amendments permit FDA to approve applications to market generic versions of brand-name drugs without repeating costly and duplicative clinical trials to establish safety and efficacy. Under the Hatch-Waxman Amendments, brand-name companies gained patent term extension to account for the time the patented product is under review by FDA and also gained certain periods of marketing exclusivity. In addition to the ANDA approval pathway, generic drug companies gained the ability to challenge patents in court prior to marketing as well as 180-day generic drug exclusivity.[3]

The generic makes one of four certifications for each patent.

Paragraph (I): That no patent information on that brand name drug has been submitted to the FDA.

Paragraph (II): That the listed patent has expired.

Paragraph (III): That the listed patent will expire on a certain date, before which time the generic will not enter the market.

Paragraph (IV): That the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the ANDA was submitted. When the generic makes a paragraph I or II certification, the FDA may approve its ANDA immediately. The FDA may approve a paragraph III certification any time after the patent's expiration date. The implications of a paragraph IV certification are not nearly as simple. A generic makes a paragraph IV certification when it does not want to wait for the expiration of the pioneer's patent rights before it begins to market its own generic version of the drug. Instead, it alleges that it is justified.[4,5]

Resources for ANDA Submissions

The following resources provide ANDA applicants with the statutory and regulatory requirements of an ANDA application, assistance from CDER to help you meet those requirements, and internal ANDA review principles, policies, and procedures. Summary tables, application forms, and other ANDA submission resources are available in ANDA Forms & Submission Requirements.

Guidance Documents for ANDAs

Guidance documents represent the Agency's current thinking on a particular topic. These documents provide guidelines for the content, evaluation, and ultimate approval of applications and also to the design, production, manufacturing, and testing of regulated products for FDA review staff, applicants, and ANDA holders.

Generic Drugs Guidances (Search "Generics" under topics)

Biopharmaceutics Guidances (Search "Biopharmaceutics" under topics)

Product-Specific Guidances for Generic Drug Development

Laws, Regulations, Policies, and Procedures

The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the United States. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; those drugs and devices are safe and effective for their intended uses; those cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations

The final regulations published in the Federal Register (a daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code of Federal Regulations (CFR). Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug applicants that are required under Federal law. The following regulations directly apply to the ANDA process.

21CFR Part 314: Applications for FDA Approval to Market a New Drug

21CFR Part 320: Bioavailability and Bioequivalence Requirements[6]

Application - ANDA Submission Process

ANDA submission process is a critical part of the regulatory approval process. ANDA should be prepared as per the FDA's recommended format. FDA has established very stringent guidelines for ANDA filing, and any minor mistake may result in the "Refusal to Receive" (RTR). RTR may cost 25% of the application fee, and ANDA should be submitted again, which will delay the approval process. In the case of Paragraph IV ANDA applications, applicants may lose 180 exclusivity.

The actual ANDA filing process begins at the stage of product development. It is crucial that ANDA applicants to make sure they have developed the Formulation to meet FDA's requirements such as IIG, Q1, Q2, the appropriate particle size of the API, and RLD /RS identification. Any mistakes during the product development stage will be a significant setback for the ANDA filing process and may result in financial loss before the product development stage applicant should obtain necessary clarification from FDA through a controlled correspondence process.

Foreign companies are also required to appoint US Agent for the ANDA filing process. U.S Agent plays a vital role in the ANDA approval process. Since the FDA communicates with foreign companies through US Agent, it remains the US Agent's responsibility to promptly communicate between the FDA and foreign companies. Delayed communication from U.S Agent may impact your ANDA approval process.

Changes in the Generic Drug User Fee Act - the legislation for drug regulation in the United States - mean that the FDA has adopted very stringent guidelines for the ANDA filing process and looks for detailed information, including technical and eCTD requirements, ahead of acceptance. Companies must demonstrate that they have implemented the regulatory requirements from the very beginning stage of product development. Time to approval depends on both the quality of the information and how it is presented.[7]

ANDA review process General provision of hatch Waxman act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (the Act). The Hatch-Waxman Amendments created section 505(j) of the Act (21 U.S.C. 355(j)). Section 505(j) established the abbreviated new drug application (ANDA) approval process, which allows lower-priced generic versions of previously approved innovator drugs to be approved and brought on the market. Innovator drug applicants must include in a new drug application (NDA) information about patents that claim the drug product that is the subject of the NDA. FDA publishes this patent information as part of the Approved Drug Products with Therapeutic Equivalence Evaluations, which is generally known as the Orange Book.

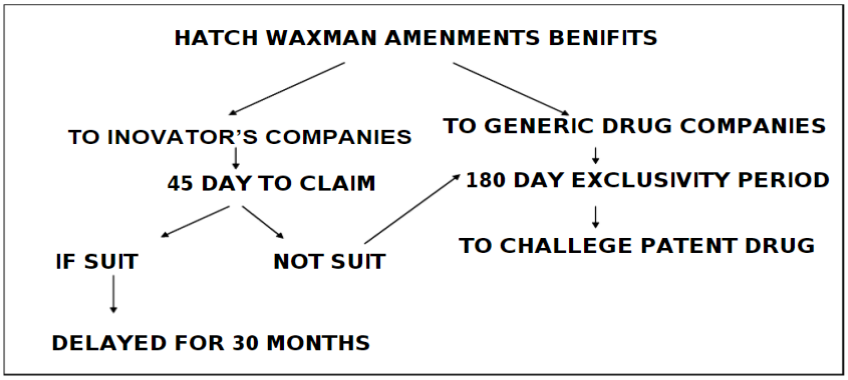

Fig 02: Hatch Waxman Amendment benefits.

PROCESS IN GENERIC DRUG DEVELOPMENT

Generic drug companies bring the generic version of the innovator/ brand drug product to the market at a substantially lower price, which benefits the public and makes healthcare more affordable. The process of bringing a generic version of an established brand name drug to market is not as simple as just copying the brand-name product. The generic company, too, must conduct certain studies, and pass strict standards set forth by the regulatory bodies.[13]

Details of Common Steps Involved In Generic Product Development

Product development processes are organized in a way that requires participation by virtually all the major functions within the organization such as strategic planning, marketing, product design, manufacturing and financial planning and budgeting .[14] Prior to generic product development a product for development must be selected. In order to properly select a product, input is needed from a variety of disciplines including:

• Research and development
• Regulatory Affairs
• Legal
• Marketing & Sales
• Finance, etc.

Depending upon the outcome from these departments the generic product to be developed is selected. But, the main driving force behind the selection of generic drug product for manufacturing is the estimated sales volume for the marketed product.[8,12]

Literature Survey: Once the product is selected generic company should to extensive literature survey, which involves the following steps.

• Study on Research and Development,
• Patent expiry,
• Data exclusivity,
• Regulatory affairs,
• Legal country requirements,
• Marketing & sales,
• Finance,
• on-line computerized search (websites etc.)

After literature survey, the selected product should be recorded into some kind of document to include information such as.

• Innovator Product Description and Dosage Form
• Innovator Product Packaging Description
• Innovator Product Sale
• Generic Product Description and Dosage Form
• Generic Product Packaging Description
• Generic Sales Forecasts
• Intended Manufacturing Site
• Intended Production Batch Size
• Any other relevant information

Based on patent expiry, product exclusivity, forecasts, availability of the active ingredient etc., the project needs to be scheduled and its' progress tracked and managed with the goal of being the first generic drug manufacturer (for that particular product) on the market.[14, 8]

ANDA Regulatory Review Process

The ANDA process begins when an applicant submits an ANDA to the OGD (Office Generic Drugs) or CDER (Centre for Drug Evaluation and Research). The document room staff process the ANDA assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist. The submitted ANDA is reviewed taking into consideration bioequivalence of the drug, chemistry and microbiology, and also the labelling. Within the first 60 days following the submission of an ANDA, a filing review is completed.[13-14]

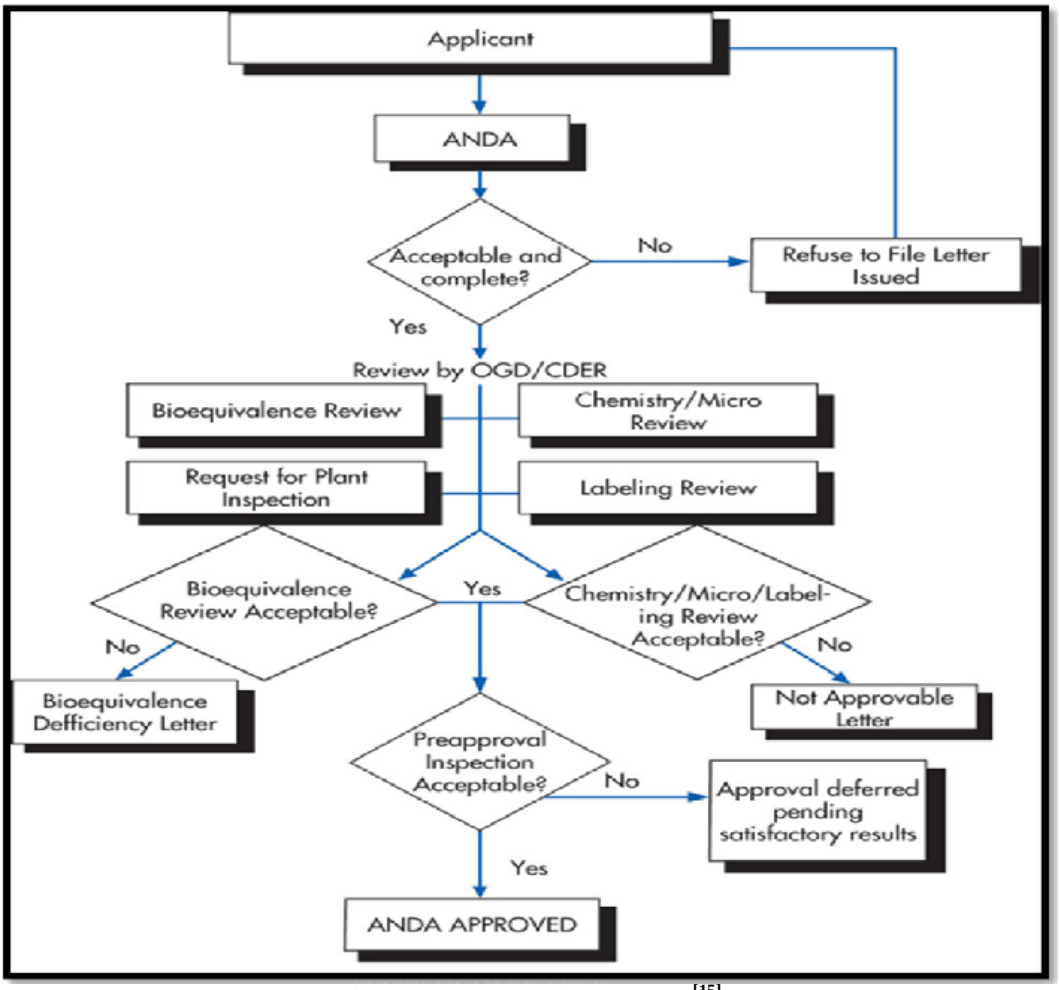

Fig. 03: ANDA Review process.[15]

Bio Equivalence Review Process

After an ANDA is accepted for filing by the RSB, the bioequivalence section is assigned to the Division of Bioequivalence (DBE) to review. For the generic drug to be therapeutically equivalent, two clinical characteristics must apply: It must be pharmaceutically equivalent as well as bioequivalent. Pharmaceutical equivalence means that the active ingredient(s), dose form, route of administration, and strength are the same for both the branded product and the generic product. Bioequivalence is when both products have comparable bioavailability when studied under similar conditions. Bioequivalence is determined by evaluation of the AUC and the maximum concentration of drug (Cmax). A generic product is considered to be bioequivalent to the branded product if the 90% confidence interval (CI) of the mean AUC and the relative mean Cmax is 80% to 125%. This criterion is the same standard used for testing the bioequivalence of branded products with reformulation or manufacturing changes.[16]

Chemistry Review Process

After an ANDA has been accepted for filing by the RSB, the Chemistry, Manufacturing and Controls (CMC) section of the application is assigned to the appropriate Chemistry Division and Team, based on the therapeutic category of the drug product. The Chemistry Divisions review the CMC section of ANDAs, Drug Master Files, Supplemental ANDAs, Annual Reports, and Controlled Correspondence. The goal of the chemistry review process is to assure that the generic drug will be manufactured in a reproducible manner under controlled conditions. After designating the chemistry deficiencies as Minor or Major, the APM faxes them to the applicant. When the application is ready for final approval, the approval package is processed through the immediate office and the applicant is contacted. Chemistry division coordinates with all disciplines prior to full approval, generates the final approval letter for office director.

Labelling Review Process

After an ANDA has been accepted for filing by the RSB, the Labelling section of the application is assigned to the appropriate labelling reviewer based on the therapeutic category of the drug product. The basis for the labelling review is to ensure that the generic drug labelling is the same as‟ the branded (pioneer) drug” labelling. After the final level administrative review and individual disciplines have resolved their deficiencies, the application will either receive a full approval or a tentative approval letter. A full approval letter details the conditions of approval and allows the applicant to market

the generic drug product. A tentative approval letter is issued if there are unexpired patents or exclusivities accorded to the RLD.[17]

EUROPE

The European Medicines Evaluation Agency is a decentralised agency of the European Union (EU). The Management Board is the European Medicines Agency's integral governance body. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU. EMA protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area, by ensuring that all medicines available on the EU market are safe, effective and of high quality. EMA serves a market of over 500 million people living in the EU.

All parties are linked by an IT network EudraNet. (EUDRANET, the European Telecommunication Networking Pharmaceuticals (European Union Drug Regulating Authorities Network), is an IT platform to facilitate the exchange of information between regulatory partners and industry during submission and evaluation of applications).

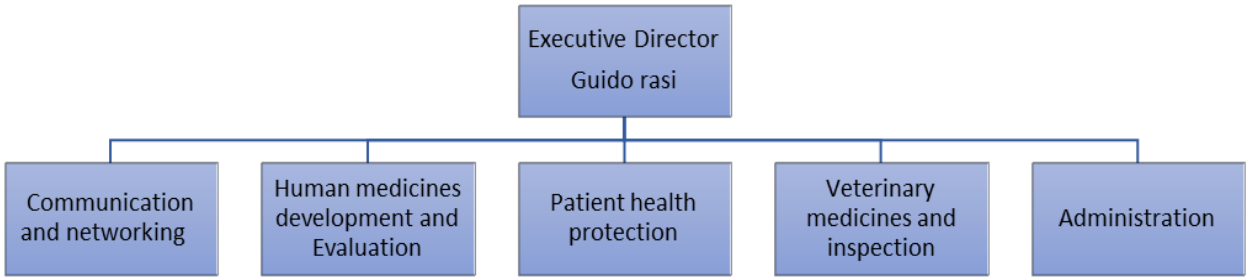

Fig. 04: EMA Permanent staff.

ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD)- The European countries established the electronic common technical document (eCTD) as their format for submissions. It is a standard derived from ICH CTD. The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission.

eCTD application An eCTD application may comprise a number of sequences. In the EU an eCTD application may comprise several dosage forms and strengths, all under one invented product name. Some review tools describe such a collection as a dossier. EGA (European Generic Medicine Association) The EGA was established in 1993. The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of Providing high-quality affordable medicines to millions of Europeans and stimulating Competitiveness and innovation in the pharmaceutical sector.[18,19]

European Medicines Agency – EMA The European Medicines Agency (EMA) is a European Union agency for the evaluation of medicinal products.

From 1995 to 2004, the European Medicines Agency was known as European Agency for the evaluation of medicinal products.

Roughly parallel to US Food and Drug Administration (FDA), but without FDA-style centralization, the European Medicines Agency was setup in1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine regulatory bodies.

Marketing Authorization: To place a medicinal on the market in the European Economic Area (EEA) a "Marketing Authorization" has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorization) or when an authorization has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a community authorization). The marketing authorization holder must be established within the EEA.

Marketing authorization procedures in EU.

I. Centralized Procedure (CP)
II. Mutual Recognition Procedure (MRP)
III. National Procedure (NP)
IV. Decentralized Procedure (DCP)[20]

Centralized procedure: The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU.

- Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.
- Application evaluated by an assigned Rapporteur.
- **Timeline:** EMA opinion issued within 210 days, and submitted to European Commission for final approval.

Centralized process is compulsory for.

- ✓ Those medicines which are derived from any biotechnology processes, such as genetic engineering.
- ✓ Those medicines which are intended for the treatment of Cancer, HIV/AIDS, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.
- ✓ Medicines officially designated 'Orphan medicines' (medicines used for rare diseases).

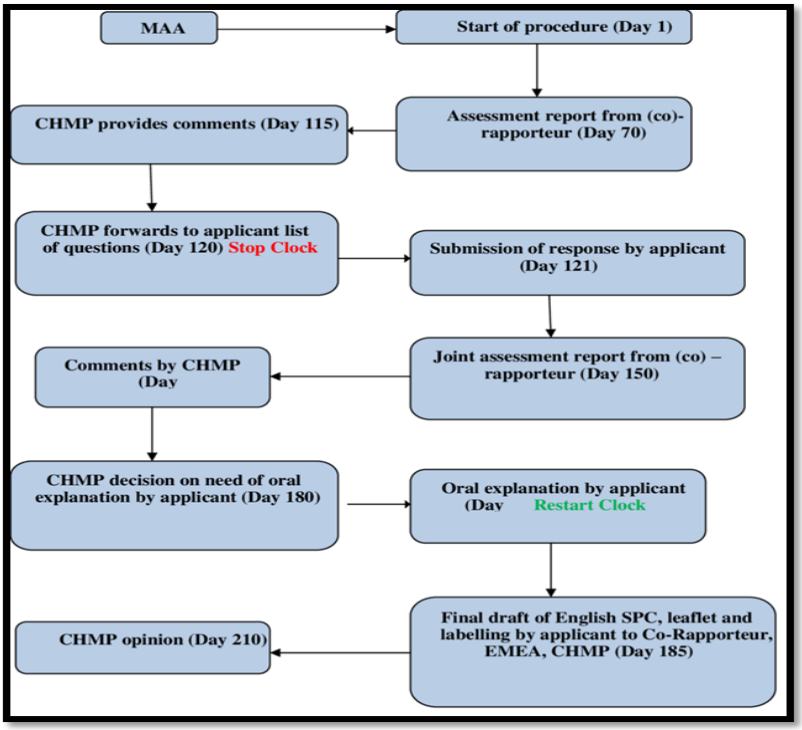

Fig 05: Centralized Procedure for Marketing Authorization in EU.

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 submits identical dossier to all EU member states in which they want marketing authorization, including required information.
- As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted.
- RMS issues a report to other states on its own findings.
- Generic industry is the major user of this type of drug approval procedure. This process may consume a time period of 390 days.

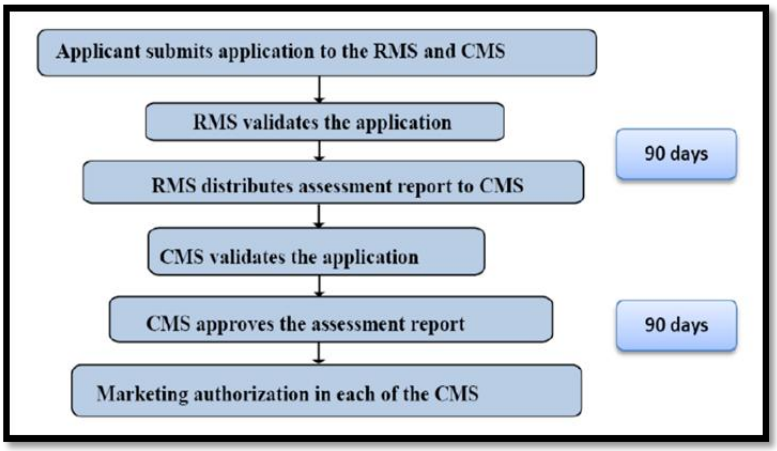

Fig. 06: Mutual Recognition Procedure for Drug Approval Process in EU.

Nationalized Procedure

the Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only.

- In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.
- New active substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure.
- Timeline for this procedure is 210 Days.

Decentralized procedure Using this procedure, companies may apply for authorization simultaneously in more than one EU country for products that have not yet been authorized in any EU country and essentially do not fall within the centralized procedure's essential drugs list.

Based on the assessment report which is prepared by the RMS & any comments made by the CMS, marketing authorization should be granted in accordance with the decision taken by the RMS & CMS in this decentralized procedure.

- Generally used for those products that has not yet received any authorisation in an EU country.
- Time: 210 days.[21,22,23]

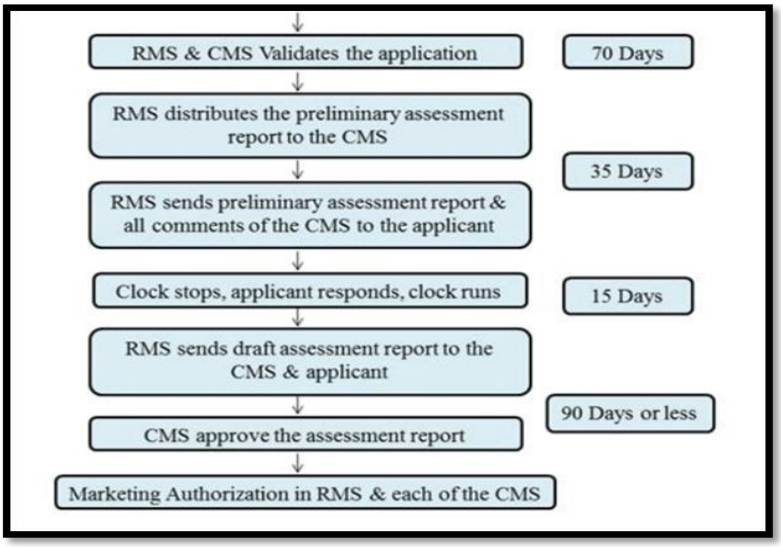

Fig. 07: Decentralized Procedure for Marketing Authorization in EU.

CONCLUSIONS

The regulatory authorities should ensure that the pharmaceutical companies comply with the FDA regulations and guidelines. There are regulations and guidelines that help in drug development, manufacture, and safety testing so that they are safe and efficient and do not harm the patient's well-being.

The drug endorsements in the USA, Europe, are the most challenging in the world. Generic drug can be approved only when the patent of Branded drug expires. Abbreviated New Drug Application process of drug approval is followed in USA where-as Europe drug approval process is more complex and summarized data.

REFERENCES

1. Abbreviated New Drug Application (ANDA) Forms and Submission Requirements | FDA
2. Generic drug. Availablefrom:http://en.wikipedia.org/wiki/Generic_drug#cite_note-0. [Accessed 28.11. 2017].
3. The Generic Drug Approval Process | FDA
4. Abbreviated New Drug Application (ANDA): Generics.Availablefrom:http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDeveloped and Approved/Approval Applications/Abbreviated New Drug Application ANDA Generics. [Accessed 28.11.17]
5. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): Preparation of product dossiers (PDS) in common technical document (CTD) format, 2017.
6. Abbreviated New Drug Application (ANDA) Forms and Submission Requirements | FDA.
7. ANDA Submission Process, Compilation, & Review | FDAbasics
8. Shargel L and Kanfer I (2005) Generic drug product development- solid oral dosage forms. Drugs and the pharmaceutical sciences series, Marcel Dekker Series, McGraw-Hill Publications: New York, pp 257-279.
9. Handbook of pharmaceutical generic development, sect. 2.22, chapter 2, oral tablets, Locum International Publishers.
10. http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-970.pdf
11. Levin M (Ed) (2001) Pharmaceutical process scale-up. Metropolitan computing corporation, East Hanover, New Jersey: Marcel Decker series.

12. Liu B. Product development processes and the importance to organizational capabilities, Massa-chusetts Institute of technology, 1994. Available from URL: dspace.mit.edu/bitstream/handle/ 1721.1/34796/57535687.pdf
13. Kashyap NU, et al. Comparison of Drug Approval Process in United States and Eur. J Pharm Sci Res, 2013; 5(6): 131-6.
14. Venkateswarlu B, et al. Regulatory Requirements for the registration of generic solid oral in USA, Singapore, Malaysia and Thailand. Journal of global trends in pharmaceutical sciences, 2014; 5(4): 2225-32.
15. Indian Journal of Pharmaceutical Education and Research Review Article www.ijper.org Regulatory Requirements and Registration Procedure for Generic Drugs in USA Naziya Ra, Sandeep DS*, Anoop Narayanan V Department of Regulatory affairs, Nitte (Deemed to be university), NGSM Institute of Pharmaceutical sciences, Paneer, Deralakatte, Mangalore, Karnataka, INDIA.
16. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): preparation of product dossiers (PDS) in common technical document (CTD) format. [Internet]. [Cited 2012 June 23]. Available from:http://apps.who.int/prequal/info_general/docu ments/generic_guide/GenericGuideli ne_PDS_CTD-Format.pdf
17. Devesh S, Vandana S, Comparative study of dossier files submission process of drug product in USA and Europe. Int J. Pharm Res Dev, 2011; 3(7): 60-78.
18. European Commission. Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period, 2007. Available from: http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf
19. European Commission Competition, EU Sector inquiry, 8 July 2009. Available from: http://ec.europa.eu/competition/sectors/pharmaceutic als/inquiry/communication_en pdf
20. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product: Preparation of product dossiers in common technical document (ctd) format. Unedited version adopted by the 45th WHO expert committee on specifications for pharmaceutical preparations. World Health Organization, 2010.
21. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare, 2008; 46-48.
22. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc, 2008; 212- 220.
23. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare, 2008; 49-51.
24. Chakraborty K. A New Drug Approval Process in Europe: A Review. International Journal of Drug Regulatory Affairs [Internet]. 15 Sept 2019 [cited 15 Sept 2019]; 7(3): 21-29. Available from: http://ijdra.com/index.php/journal/article/view/332.
25.