Current Status of Generic Drug Approval Process in USA and EU

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Abstract : A generic drug is more efficient, safe, and low cost alternative of the innovator or branded drug in the market. Generic drugs are marketed after the expiry of the patented drugs. ICH process Common Technical Document (CTD) has been developed for standardized structure for regulatory submission that is acceptable in all ICH countries. There are few differences in the dossier submission for various regions. Aim of this study is to understand the current generic drug approval process in the regulatory market of USA and EU. Abbreviated New Drug Application (ANDA) can be filed to the regulatory authorities, to get generic drug approval. Under section 505(j) of Hatch-Waxman Act, ANDA may be filed for any generic version of the reference listed drug where as generic drugs in EU approved under the marketing authorization. After analysing the various requirements for the generic drug approval in the above stated countries, it was concluded that the regulatory guidelines of Europe was not well defined but FDA gives very much well defined requirements.

***Index Terms*- Generic Drug, USA, ICH, ANDA, Generic Drug Approval**

1. INTRODUCTION:

A generic drug is a pharmaceutical drug which is defined as, "A generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use."A generic drug product, also referred to as a multisource pharmaceutical product, is considered to be ''essentially similar'' or bioequivalent to an innovator (brand name) product. Bioequivalence implies that a generic drug product is essentially identical to the brand name (reference) drug product in terms of active ingredient(s), strength, dosage form, route of administration, quality, safety, efficacy, performance characteristics, and therapeutic indication. It should contain the same active ingredients as the original formulation but it may differ in characteristics such as manufacturing process, formulation, excipients, color, taste, and packaging.

According to the FDA, generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetics and pharmacodynamics properties. Generic drugs are allowed for sale after the expiry of the patent of the original drugs. Because the active chemical substance is the same, the medical profile of generics is believed to be equivalent in performance. Although they may not be associated with a particular company, generic drugs are usually subject to government regulations in the countries in which they are dispensed. They are labeled with the name of the manufacturer and a generic non-proprietary name such as the United States Adopted Name or international non-proprietary name of the drug.

❖ **Basic requirements of generic drug product:**

- Contain the same API as the innovator drug (inactive ingredient may vary)
- Be identical in strength, dosage form, and route of administration to RLD
- Have the same use indications as RLD
- Be bioequivalent to RLD
- Meet the same batch requirements for identity, strength, purity and quality
- Be manufactured under the same strict standards of FDA's GMP regulations required for innovator products

USFDA: In USA, Food and Drug Administration (FDA) is the drug regulatory authority for approving food, human and veterinary drug products that are to be marketed in USA. Drugs, including: prescription drugs (both brand-name and generic) non-prescription (over-the-counter) drugs.

EMA: In EU, European Medicines Agency is the regulatory agency for approving human and veterinary drug products centrally to market the drugs in European Union (EU). There is also individual National Competent Authorities (NCA) for approving the drug products in individual states.

2. GENERIC DRUG APPROVAL PROCESS IN USA:

❖ **Hatch – Waxman Act:**

An Act commonly known as The Drug Price Competition and Patent Term Restoration Act of 1984 was thought to be the answer to the rising drug prices and was deemed to be a compromise between the two competing players in the pharmaceutical market-generic manufacturers and brand name manufacturers. The Act incorporates a benefit for each side. The brand name manufacturers were benefited by the Act's patent restoration provision. The generic manufacturers were benefited by the Act's streamlining of the regulation approval process and allowing immediate competition in the marketplace upon patent expiration by

allowing an exemption from infringement activities relating to FDA submissions for generic drugs. The Hatch-Waxman Act attempted to balance the public interest of faster access to cheaper generic drugs against the research industry's financial incentive to discover a new drug product.

❖ **General Provisions of the Act**
- Maintaining list of patents which would be infringed.
- Only Bioavailability studies and not clinical trials needed for approval.
- Para I, II, III and IV certifications
- Data exclusivity period for New Molecular Entities.
- Extension of the original patent term.
- The "Bolar" Provision

❖ **Recent additions to the Hatch-Waxman Act**
- Non-extension of the 30-month period.
- Time limit for informing patent owner.
- Provision for allowing declaratory judgment.
- Benefit of exclusivity for several ANDAs filed on same day allowed

❖ **Types of Certifications:**

As per the Hatch Waxman act, generic drug applicants should include certifications in their applications for each patent listed in the "Orange Book" for the innovator drug.

This certification must state one of the following:

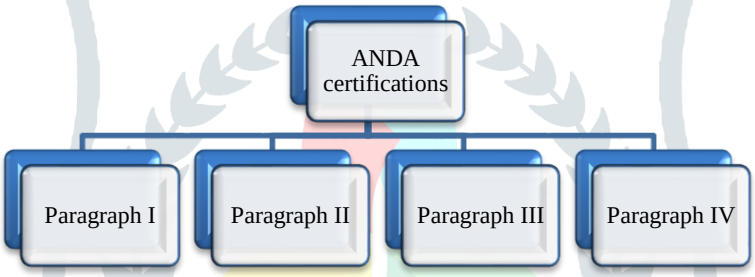

Table 1 Types of certifications

TYPE	PATENT CERTIFICATION	ANDA FILING
Paragraph I	The drug has been patented.	If a generic drug manufacturer certifies I & II, then the FDA starts processing the generic ANDA right away
Paragraph II	The patent has already expired.	
Paragraph III	The generic drug will not go on the market until the day of expiry of the patent	If a generic drug manufacturer certifies 3, then the FDA starts processing the ANDA, and gives approval when the patent expires
Paragraph IV	The patent is not infringed or is invalid	ANDA filer notifies patent holder within 20 days – Patent holder must sue for infringement within 45 days– If the patent holder sues, FDA must withhold approval for 30 months (one time only) – If the patent holder does not sue, FDA may approve ANDA at any time– If a court rules that the patent is not infringed or invalid, FDA may proceed after decision. – If first generic ANDA files will gets 180 days exclusivity (per product)

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.

❖ **Abbreviated New Drug Application (ANDA) Forms and Submission Requirements:**

The FDA aspires to assist applicants in developing abbreviated new drug applications (ANDAs). To facilitate the development of an ANDA, agency provides the following resources on ANDA forms and submission requirements.

➢ **ANDA Forms:**

In order to submit a complete ANDA, applicants should review the following forms and prepare all that are required for your specific application.

- Filing Review of ANDAs MAPP including filing checklist
- Form FDA-356h: Application to Market a New Drug, Biologic, or Antibiotic Drug for Human Use
- Form FDA-3794: GDUFA Cover Sheet
- Form FDA-3674: Certification of Compliance
- Generic Drug User Fee Payment Information
- Drug Master Files (DMFs)

➢ **Requesting a Pre-Assigned ANDA Number:**

Applicants may request a pre-assigned ANDA number ONLY when submitting a new ANDA. If you are converting an established ANDA to eCTD, you MUST use the original ANDA application number. For further guidance, please view Requesting a Pre-Assigned ANDA Number or email CDERAPPNUMREQUEST@fda.hhs.gov.

1. Before you request a pre-assigned application number, apply for a secure email with the FDA by contacting secureemail@fda.hhs.gov. If using a US Agent to request the number, please be sure that the agent has established a secure e-mail.

2. Send one email per application number request to cderappnumrequest@fda.hhs.gov. Please note that at this time the Electronic Submission Gateway (ESG) cannot accept requests for pre-assigned numbers.

Include the following information in your e-mail:

➢ **Subject:** Request for a Pre-Assigned <*insert Application Type*> Number
➢ **Text:**
  - Name of Applicant that will be on form (FDA 1571 or 356h) or transmittal letter (Master File)
  - Applicant Address (street, city, state, zip code)
  - Name of US Contact, Phone Number, Fax Number, Email Address
  - Name of drug or Subject of Master File <insert Established Drug Name (if applicable); or sponsor code name with short description of product, Dosage Form, Strengths if applicable >
  - Drug Trade Name (if applicable)

If requesting for an ANDA, please include the following:

➢ Reference Listed Drug Name and RLD Number

➢ Is there a NCE exclusivity? YES or NO

- If yes, when does it expire?

➢ Have you filed any applications for this active ingredient before? If YES, answer question below
- Please specify the ANDA Number, Drug, Dosage Form, Strength

➢ A pre-assigned number will be issued within 3 business days.

❖ **Electronic Submissions:**

- The FDA no longer accepts paper ANDA submissions.
- All ANDA submissions MUST be in eCTD format. eCTD submission sizes 10 GB or less must use the FDA Electronic Submission Gateway (ESG).
- If an eCTD submission is greater than 10 GB, it may be submitted via physical media (DVD/USB Drive) to the CDER Document Room or via ESG.
- Please see the guidance for industry "Transmitting Electronic Submissions Using eCTD specifications" for details. This document and other eCTD related guidance and specifications are available on the FDA eCTD website.

❖ **Abbreviated New Drug Application (ANDA) filing checklist for documents**

- Following documents are prime requirement for Application as per E- CTD Modules:
- **Module –I – Administrative**

a. Form 356 h, b. Form FDA 3674 , cover letter c. field copy certification , debartment certification , financial certification , patent information

b. Module –II, III, IV: Quality overall summary (QOS) (documents related to drug substance and Drug product) and clinical documents.

❖ **Drug substance related documents**

- Drug substance approved vendor documents with approved DMF including all required declarations /certifications from drug substance manufacturer as listed below.
  - cGMP Certificate, Genotoxicity certificate. TSE/BSE Certificate, GMO Certificate, Metal Catalyst Declaration, Melamine Certificate, Residual Solvent Declaration, Access on CEP, Debarment Certificate, CEP Attestation, Elemental Impurity Assessment.
- Approved Drug substance specification
- Certificates of analysis for both drug substance and drug product manufacturer with complete sets of chromatograms/histograms /difractograms.

❖ **Drug Product related documents**

- Executed BMRs and BPR for all strengths to be applied.
- Intended BMRs and BPRs for all strengths to be applied.
- Specifications/ Standard testing procedures :
- Excipients specifications
- Packing material specifications
- In-process specifications
- Finished product specifications
- Stability specifications
- Certificates for analysis for Drug substance manufacturer and Drug product manufacturer
- Excipient COA
- Packing material COAs
- Purified water COAs used for batch execution
- In-process COAs
- Finished product COAs with complete sets of chromatograms
- Packaging Material IR, Drawing, Vendor qualification data/ Technical data Sheet, component
- specification& Test data and Food Grade Certificate (for new vendor) with all required certificates as listed below
- Declaration/Certificate FP
- cGMP Certificate
- Debarment Certificate
- Reconciliation Summary Sheet-Strength wise
- Sample Availability statement for drug product
- Comparative list of equipment's (Exhibit Vs. Intended)
- Reprocessing Statement
- Post approval Stability Commitment
- Conviction statement
- Environmental Impact Analysis Certificates

❖ **Validation requirements:**

- Manufacturing Process
  - Process validation protocol and reports for exhibit batch and also for intended commercial (proposed)

- Analytical process
  - API verifications for applicable parameters as per specifications
  - Drug product validation for applicable parameters as per specifications
  - Hold time protocols and reports

- Stability Study
  - Pre-approval Stability protocols /photo stability protocols
  - Stability summary for pre-approval, post approval ,photo stability (ACC, long term and photo stability)
  - Post approval stability commitment
  - Reference/Working Standard

- Reference/Working Standard (used in verification/ validation and analysis of drug substance and drug product as listed below:
  - Reference Standard - Certificate of Analysis
  - Working Standard - Certificate of Analysis, Characterization / qualification data
  - Impurity Standard - Certificate of Analysis, Characterization / qualification data
  - Reference standard and Working Standard Individual Spectra/Chromatogram
  - Reference standard and Working Standard - Overlapping Spectra/Chromatogram
  - Comparative Multimedia Dissolution Profiling for generic drugs vs. innovator drug
  - Moisture vapor transmission report for packing components

- Uniformity of dosage unit by content uniformity using Stratified sampling if Applicable
- Microbial limits validation study for Drug substance and drug product
- Transport study protocol if applicable

❖ **Clinical study documents**
Bio-equivalence study report for selected pivotal batch for IP (investigational drug product) and Reference listed product.

❖ **Checkpoints for review of documents before submission to avoid RTR**
The following type of deficiencies that FDA considers to be major or minor deficiencies:

❖ **Form FDA 356h (356h)**
An ANDA must contain a completed application form (i.e., Form FDA 356h). If this form is not included, or is not signed, which indicates that the applicant is not attesting to the material contained in the application, FDA will RTR the ANDA?

❖ **Submission, Format, and Organization**
The ANDA should be formatted according to the eCTD format, and it should be submitted electronically for GDUFA metric goals to apply to the ANDA.
21 Under Section 745A(a) of the FD&C Act, electronic submissions of applications to FDA will be required at least 24 months after the issuance of the final guidance for industry, Providing Regulatory Submissions in Electronic Format-Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (the eCTD guidance e), which published on May 22.

❖ **Non-Payment of GDUFA Obligations**
FDA will RTR an ANDA in certain cases if there are outstanding user fee obligations

- If an applicant fails to pay the GDUFA ANDA or PAS fee within 20 calendar days of submitting the application 24
- If an ANDA references a Type II active pharmaceutical ingredient (API) Drug Master File (DMF) that is not on the public available for reference list because of non-payment of the GDUFA DMF fee
- If an ANDA references a facility that is on the facility arrears list for failure to pay the GDUFA facility fee(s)
- If the applicant is the owner of or is affiliated with the owner of a facility on the facility arrears list
- If the applicant is listed on the backlog arrears list
- If the applicant is affiliated with an applicant on the backlog arrears list.

In all of these cases, FDA will RTR an ANDA for nonpayment of GDUFA user fee obligations. Upon satisfaction of all applicable user fee obligations, CDER's Office of Management will issue a formal correspondence to the applicant Indicating the adjusted receipt date (i.e., the date on which all outstanding user fee obligations were satisfied in full) for which the ANDA is eligible.

- Lack FDA wills RTR an ANDA in certain cases if there are outstanding user fee obligations:
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  - If an ANDA references a Type II active pharmaceutical ingredient (API) Drug Master File (DMF) that is not on the public available for reference list because of non-payment of the GDUFA DMF fee
  - If an ANDA references a facility that is on the facility arrears list for failure to pay the GDUFA facility fee(s)
  - If the applicant is the owner of or is affiliated with the owner of a facility on the facility arrears list
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- Lack accordance with 21 CFR 314.93 and 10.30, and the suitability petition is approved by FDA. The changes (from the RLD) that can be requested in a suitability petition are:
  - Change in route of administration
  - Change in dosage form
  - Change in strength
- One active ingredient is substituted for one of the active ingredients in a listed combination drug An applicant who wishes to rely on an approved suitability petition as the basis of submission for an ANDA can do so by identifying the listed drug cited in the approved petition as the basis for the ANDA, subject to the limitation described in 21 CFR 314.93(f)(2).
  - In addition, the docket number and a copy of FDA's correspondence approving the petition must be included in the ANDA submission.

❖ **Common Technical Document (CTD):**

CTD is a common technical document, it is a harmonized document introduced by the ICH in order to avoid any duplication and easier translation into regional languages in a single application. CTD makes it easier to submit one single application to more than one country at the same time for registration of the drug product. According to ICH, all the technical requirements for the application of drug approval were harmonized in CTD format which is scientifically more elaborate by USFDA in Quality Overall Summary (QOS) and Overall efficacy (includes a clinical overview and clinical summary). This has improved the presentation of the registration documents has expedited the efficiency in the FDA review process.

The main Areas of Harmonization for CTD are:

- Safety pharmacology
- Clinical pathology
- Immunotoxicology
- Juvenile toxicology studies
- Statistical methods in certain studies like mutagenicity, carcinogenicity and toxicokinetic studies during

The Common Technical Document is organized into five modules. The contents of Module 1 are different according to the competent authorities' of the United States (FDA), the European Agency for the Evaluation of Medicinal products (EU). The modules are present in the triangular format which all the modules are the part of CTD. Module 1 is not the part of CTD it is different for different countries. The different modules are as follows:

Module 1: This module is specific to each region and is usually not part of the CTD. It contains all the **administrative information** and prescribing information (package inserts and labeling) with respect to the regulatory agency of that particular country.

Module 2: It consists of the overviews and overall summaries of the CTD. **Quality overall summaries**, clinical and non-clinical overview and summaries are included in this module. Pharmacology, pharmacokinetics, toxicology studies which are important to prove the safety and efficacy of the drug.

Module 3: Quality – It covers the complete pharmaceutical and technical aspects which can affect the quality of the drug product. From the formulation and development department (pharmaceutical development report) to the manufacturing (GMP), analysis and testing (GLP), packing, storage conditions, stability studies of the product.

Module 4: Non-clinical study reports – It covers the complete pharmacological, toxicological study reports and information equivalent to the quality of the drug to provide the evidence of the safety of the drug product.

Module 5: Clinical study Reports – The results of various clinical trials on human beings and the reports listing the desired effect of the drug product are mentioned in this part. This part proves the efficacy of the drug to the regulatory authorities. Bioequivalence studies are conducted on healthy volunteers to prove the bioavailability similarity between the both generic and innovator drugs.

❖ **Recommendations for e-CTD**

1. PDF Files with version 3.0 of Acrobat Reader

2. Use of Embedded fonts in the Portable Document Format
3. A Print area of 8.5 inches by 11 inches and margin of 1 inches is ensured on sides.
4. Scanned Documents should be avoided as Source Documents.
5. Hypertexts can be indicated by Blue-Texts or by rectangles using thin lines.
6. Numbering on the PDF and Documents should be included as same.
7. Security or Passwords should not be included.
8. Full Indexes should be included.
9. Electronic Signatures may be added, Procedures are being employed for archival of the same

❖ **ANDA Review Process**

- Applicant will select the generic product and innovator for ANDA submission along with certification clause.
- Submission requirement shall be followed as per requirement of respective clause selected for product.
- Applicant shall ensure the Hatch-Waxman Act for generic drug vs innovator as per Drug Price Competition and Patent Term Restoration Act of 1984 considering recent addition to act also.
- Applicant shall compile the dossier as per e CTD modules considering the guidance for ANDA format.
- After Fee payment as per GDUFA, Applicant shall apply complete set of dossier along with all required submission forms as listed in next section.
- Once applied by Applicant, Agency reviewer team will review as per their standard guidelines and norms.
- Upon finding of discrepancies/queries, Agency will issue IR (information request), CR (complete response letter),
- DRL (Discipline review letter) based on criticality of observation and Applicant has to respond the same within stipulated timeline to have successful submission and approval.
- If USFDA Agency will feel any critical observation under RTR, they will refuse the application and can issue Warning letter too and again Applicant has to respond the same within stipulated timeline to have successful submission and approval.

❖ **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.

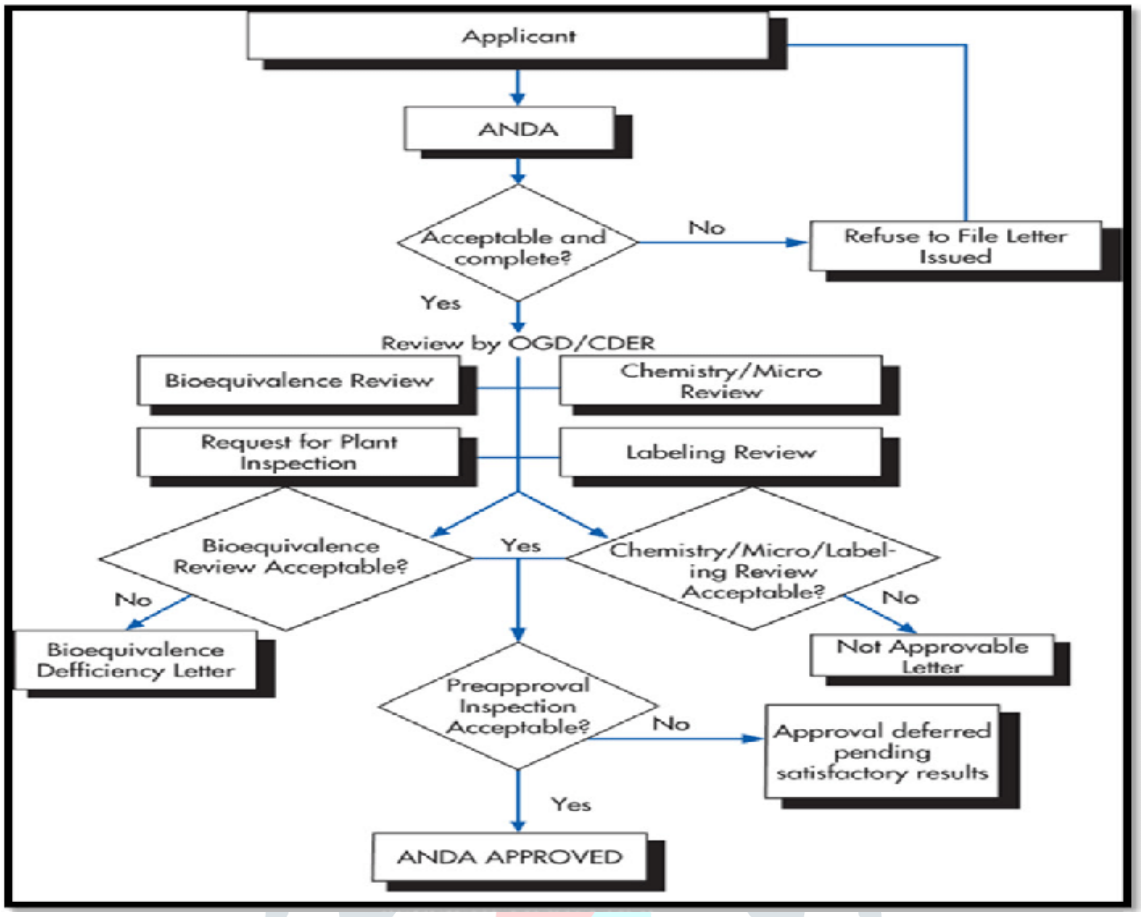


Fig. 1 Flow chart of ANDA Review process

❖ **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.

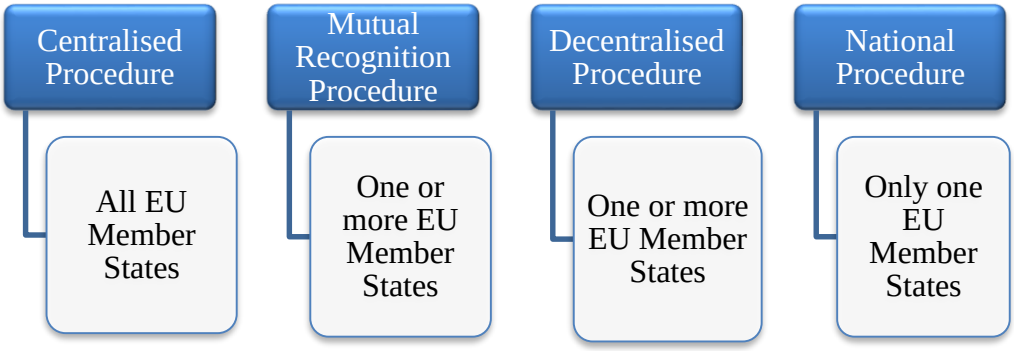
Chemistry division coordinates with all disciplines prior to full approval, generates the final approval letter for office director.

❖ **Labeling Review Process**

After an ANDA has been accepted for filing by the RSB, the Labeling section of the application is assigned to the appropriate labeling reviewer based on the therapeutic category of the drug product. The basis for the labeling review is to ensure that the generic drug labeling is the same as‟ the branded (pioneer) drug” labeling. 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.

3. GENERIC DRUG APPROVAL PROCESS IN EU:

❖ **Marketing authorization procedures in EU:**



❖ **Nationalized Procedure (NP):**

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.

❖ **The Mutual Recognition Procedure (MRP):**

To be eligible for the mutual recognition procedure, a medicinal product must have already received a marketing authorisation in one EU country. Basic arrangements for implementing the mutual recognition procedure laid down in Directive 2001/83/EC have been made in all EU countries.

An application for mutual recognition may be addressed to one or more EU countries. The applications submitted must be identical, and all EU countries notified. The country charged with evaluating the application or Reference Member State notifies the other Concerned Member States. The Reference Member State is then charged with deciding on the product.

This evaluation process may take up to 210 days, and ends with the granting of a marketing authorisation in that EU country. The Concerned Member States then have 90 days to recognise the decision of the Reference Member State, and the summary of product characteristics, labelling and packaging. National marketing authorisations are granted within 30 days.

Should a country refuse to recognise the original national authorisation, the issue is referred to a coordination group (CMDh) which should reach a consensus within 60 days. If none is reached, the procedure is submitted to the appropriate EMA scientific committee (CHMP), for arbitration. The opinion of the EMA Committee is then forwarded to the Commission.

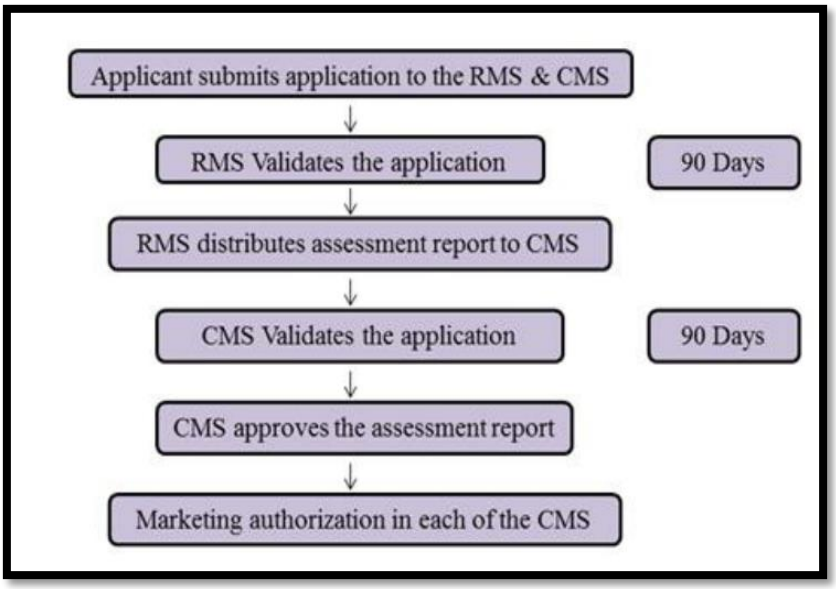


Fig. 2 Flow chart of Mutual Recognition Procedure

❖ **The Decentralised Procedure (DCP):**

The Decentralised Procedure was introduced by Directive 2004/27/EC. It allows the common assessment of an application submitted simultaneously to several Member States. One of the Member States will take the lead in evaluating the application as reference Member State.

At the end of the procedure, the draft assessment report, SPC, labelling and package leaflet, as proposed by the Reference Member State, are approved by the other (concerned) Member States. Should a country refuse to approve the assessment, the issue is referred to a coordination group which should reach a consensus within 60 days. If none is reached, the procedure is submitted to the appropriate EMA scientific committee (CHMP), for arbitration. The opinion of the EMA Committee is then forwarded to the Commission.

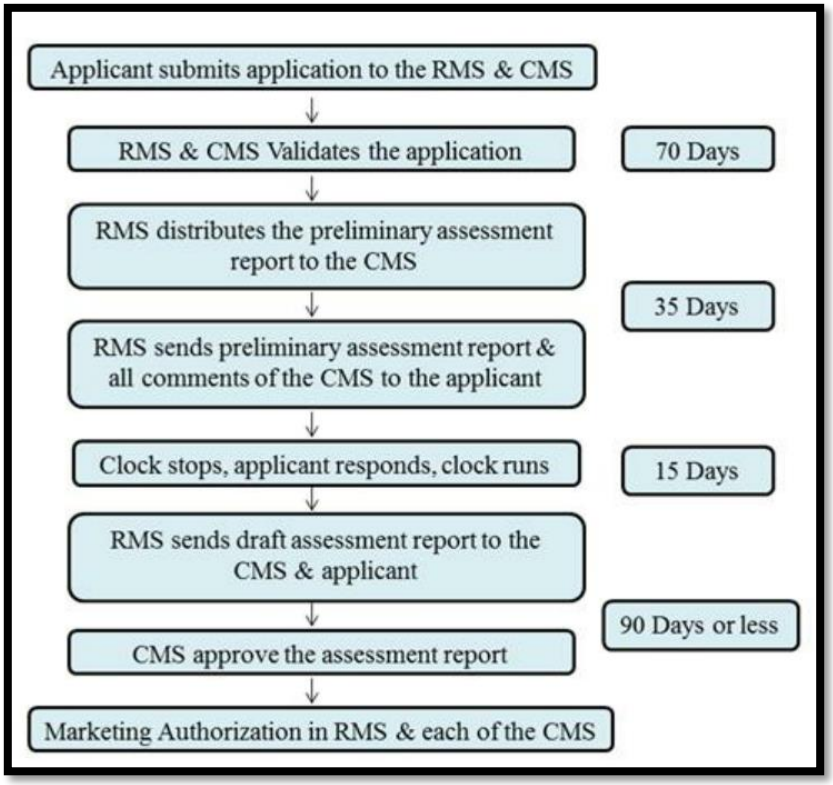


Fig.3 Flow Chart of Decentralised Procedure

❖ **Centralised Procedure:**

European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure). Marketing applications for drugs for use in humans are evaluated by the Committee for Medicinal Products for Human Use (CHMP).

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

- biologic drugs developed by recombinant technology,⎪ controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods
- medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases
- orphan medicinal products
- Other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

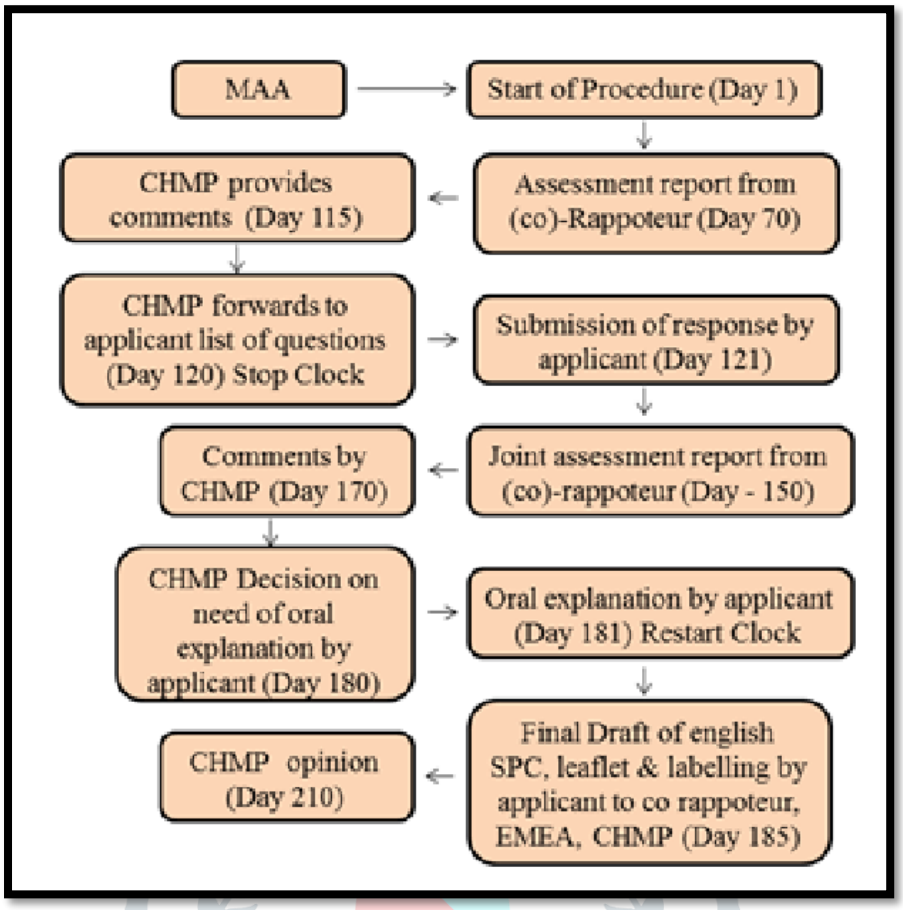


Fig. 4 Flow Chart for Centralised Procedure

❖ **Pre-submission meetings**

- At least seven months before submission, applicants should notify the EMA of their intention to submit an application. In that notification applicants should include:
- A draft summary of product characteristics
- A justification of the product's eligibility for evaluation under CP.
- An indication on the number of strengths / pharmaceutical forms / pack sizes (if already known).

❖ **Admissibility to the centralized procedure**

The applicant's request for eligibility for evaluation via the centralized procedure justification and summary of product characteristics/product profile from the applicant will be presented to all CHMP members at the subsequent CHMP meeting Following discussion at CHMP, the EMEA will then inform the applicant of the CHMP position as to whether the product is eligible for evaluation via the centralized procedure.

❖ **Selection of Rapporteur/Co-Rapporteur**

For any scientific evaluation in respects of a procedure a Rapporteur, and if relevant a Co-Rapporteur shall be appointed. The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP. Requests for Rapporteur/Co- Rapporteur appointment should optimally be provided seven months before the intended submission date, and should arrive at the EMA at least 2 weeks in advance of the CHMP meeting.

❖ **Submission of the application**

The date and time of delivery of the dossier to the EMA should be arranged between the applicant and the EMA. The EMA will inform future applicants well in advance of the program of scheduled CHMP meetings in order to be able to identify preferred optimal submission dates. As soon as the applicant is aware that the original indicated submission date cannot be met he should inform the EMEA, Rapporteur and Co-Rapporteur immediately, since a delayed submission can have consequences for already planned activities of the assessment teams of the Rapporteurs and Co- Rapporteurs. It may even be the case that assessment capacity is not immediately available at the moment a delayed submission is received and that therefore Rapporteur and/or Co-Rapporteur may in exceptional cases request the appointment of a new Rapporteur and/or Co-Rapporteur.

❖ **Dossier to be submitted:**

The EMEA requires from the applicant:

- One full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File, if any;
- Two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labelling and package leaflet in English;
- One electronic copy of module 1 and 2 (at least 2.1-2.5) in WORD.
  In addition, applicants must submit the dossier to both the Rapporteur and the Co-Rapporteur in parallel to the EMEA. Otherwise there may be a delay in the start of the procedure because of the time lapse between the validation by the EMEA and the confirmation from the Rapporteur and the Co-Rapporteur that they have received the dossiers.

❖ **Validation by the EMA**

During validation the EMA Product Team Lead (PTL) consults the Rapporteur and Co-Rapporteur, on the need for action relating to matters such as GMP inspection, ad-hoc expert groups, Scientific Advisory Groups, GCP inspections, and completeness of data. In the event that the EMA requires additional data, information in order to complete its validation of the dossier, it will contact the applicant requesting supply of
this data, information or clarification within a specific time limit.

❖ **Positive outcome of the validation**

In case of a positive outcome, the EMEA shall notify the applicant in writing that the validation has been successfully completed, together with the names of CHMP members to whom full or partial copies of the dossier should be sent.

❖ **Negative outcome of the validation**

Failure to provide the data, information or clarification requested, failure to adhere to the EU CTD format will result in a negative validation, of which the applicant shall be informed in writing. The applicant will be invited to either collect the dossier or have it destroyed by the EMEA.

❖ **Inspection Reports**

The inspector provides a report with comments on major factual errors within 15 days. The final report is sent to EMA inspection sector by day 180 at the latest, and circulated to the rapportuer and co-rapportuer and CHMP.

4. CONCLUSION:

Generic Drug manufacturing is a major part of the pharmaceutical industry and grow rapidly because to the patent expiry of the branded drugs. In the present study, an attempt was made to search the current status of generic drug in regulatory environment of USA and EU. Generic drug manufacturers may file an Abbreviated New Drug Application (ANDA) that incorporates the safety and effectiveness data submitted by original innovator drug manufacturer and adds only bioequivalence studies. Hatch – Waxman Act has generally achieved the dual goal availability of cheap drugs to consumer and providing incentives to innovator pharmaceutical drug manufacturers to continue producing innovative drugs. Hatch Waxman Act established a regulatory framework to balance, to entry of generic drugs by providing incentives to brand name companies. It has been found that USA has the most stringent regulation for generic drug filing in the world. The regulatory authorities should ensure that the pharmaceutical companies comply with the FDA regulations and guidelines. CTD provides a globally harmonized format that is accepted in many regions, avoiding the need to compile different registration dossiers for different regulatory authorities. Hence, EU has adopted 4 marketing authorization procedures for the generic drug approval, the sponsor can apply for approval through any one procedure based on his drug. Europe safeguards the public health by assessing the medicines to their rigorous scientific standards. It is concluded that USA have the toughest drug approval standard in the world. Unlike USA, the regulatory guidelines of EU are not that much well defined. One cannot draw or get desired requirements for approval from official sites of this country. But FDA gives very much well defined requirements.

5. ACKNOWLEDGEMENT:

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