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" Regulatory Requirements For Drug Approval Process In India, United States of America and European Union"

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ABSTRACT:
The article explores drug approval processes in the US, Europe, and India. It outlines the rigorous research and development required for new drugs, covering areas like chemistry, manufacturing, preclinical science, and clinical trials. Regulatory agencies in each country, suchastheFDA,EMA,andCDSCO,reviewdatatoensuresafety,efficacy,andqualitycontrol. Country-specific regulatory authorities enforce rules and issue guidelines for drug marketing. Variations exist in approval procedures, reflecting differences in healthcare systems and legal frameworks. The article aims to provide insights into how regulatory agencies evaluate new drugs to protect public health across diverse global contexts.

I. INTRODUCTION:

Each country has unique regulatory requirements for approving new drugs, making it challenging to adopt a single approach for global approval. Therefore, understanding the regulatorylandscapeofvariouscountriesisessential.TheUnitedStatesofAmerica(USA)and the European Union (EU) are prominent global markets for pharmaceuticals, prompting companies to focus on their regulatory frameworks. This article examines the regulatory strategies of the USA, EU, and India, providing insights into navigating drug approval processes in these key regions.[4]

The drug development process begins with lead molecule identification for a target disease, followed by optimization. Pre-clinical trials on animals ensure safety and efficacy before seeking permission from the competent authority of a country for clinical studies. Clinical trials, conducted in four phases, ascertain safety, efficacy, and optimize the drug dose in humans. Subsequently, a marketing authorization application (MAA) is submitted, subject to approval by the competent authority if the drug meets safety and efficacy requirements, with benefits outweighing risks. This process, depicted in Figure 1, spans approximately 15 years from discovery to approval. [4]

DrugapprovalprocessinIndia:

Currently, different nations haveto adhereto various regulatory standards in order to approve new drugs. A single Marketing Authorization Application (MAA) Regulatory strategy is applicableinmanynationsandisnearlyadifficulttask. Consequently,itisimperativethatyou awareness of the legal requirements for each MAA nation.

An application for authorization to commercialize a new medicine, or novel product, is called a new drug application (NDA), and it is filed to the relevant regulatory body.Asponsor must provide preclinical and clinical test results, a description of manufacturing trials, and drug information in order to be granted approval.

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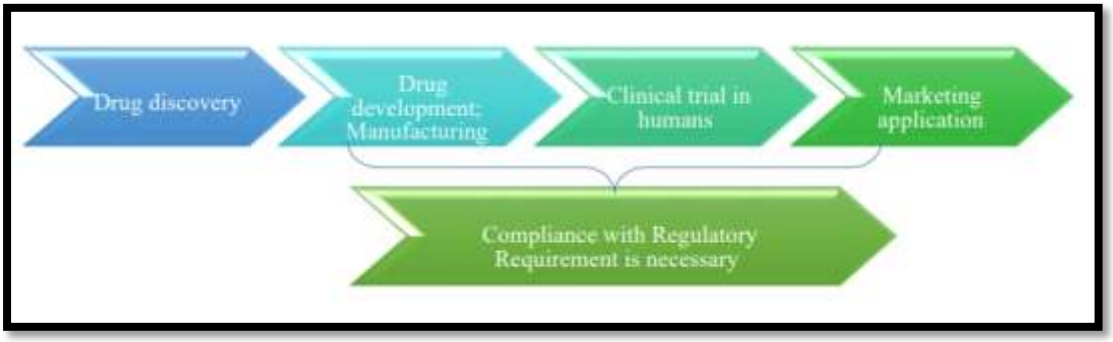

Fig.(1)BasicDrug Regulation.

Pre-clinicalresearch,
Clinicaltrials:
Themanystagesofclinicaltrials include:

1. PhaseItrials:Human Pharmacology
2. PhaseIItrials: Exploratory trials
3. PhaseIIItrials:confirmatory studies4.PhaseIVtrialsafter commercialization.

Following receipt by the agency, the NDAgoes through a technical transfer. This evaluation attests to the fact that sufficient data and information have been provided in every field to support "filing" the application.
Threeoptionsareavailableforsendingan NDAtothesponsorafterithasbeen reviewed:

1) Not approved: include a list of shortcomings and an explanation of reasonsChanges are acceptable, and a promise to do post-approval research may be requested.
2) Approval:Itindicatesthatthemedicationisauthorized.
3) Approvable:Shouldtheconductperformedbedeemedeitherapprovableornot,thenornot, thenthe regulatory authority gives the applicant the chance to meet with the agency to go over the shortcomings.[1]

IndianRegulatoryRequirements:

1] CentralDrugsStandardControlOrganization(CDSCO):

The Drug and CosmeticsAct assigns some responsibilities to the federal government, which are to be fulfilled by the central drug authority, or CDSCO. The CDSCO headquarters are in New Delhi, and it is run by the Ministry of Health, the General Directorate of Health Services, and the Ministry of Health's Family Control. Indian government's Family Directorate General of Health Services Welfare.The primary objectiveofadrugregulatorybodyistoensurethatdrugs thatareimported,produced, and licensed Pharmaceuticals have appropriate levels of effectiveness, safety, and quality.

2] DrugControllerGeneralofIndia [DCGI]

The drug controller general of India is in charge of the central drug standard control organization,whichisinchargeofregulatingbothmedicaldevicesandpharmaceuticals inIndia.Heorsheisresponsibleforauthorizingclinicalstudies,newdrugs,andmedical equipment.becompletedinIndia.Heisappointedbyfederallawunderthestate'sDCGI drugcontrolprogram.There'llbeefficientarrangement.TheDCGIreceivesinputfrom thedrugconsultationgroup(DCGI)andthedrugtechnicaladvisoryboard(DTAB).[2]

IndianDrugApprovalProcedure: TheIndianparliamentestablishedtheDrugandCosmetic Act 1940 and Rules 1945 to control the import, manufacturing, sales and distribution of medicationsandcosmetics.TheofficeoftheStandardControlOrganization's(CDSCO)chief, It was decided to create the Drugs Controller General (DCGI). In 1988, the Schedule Y was added by the Indian government to the Drug and Cosmetics 1945 Rules. ScheduleYcontains the instructions and specifications for clinical trials, which underwent additional revisions in 2005 to align with globally recognized protocol. When an Indian business desires to when producing or importing a novel medication, one must request for authorization from the licensing body (DCGI) submitting Form 44 together with the information [2].

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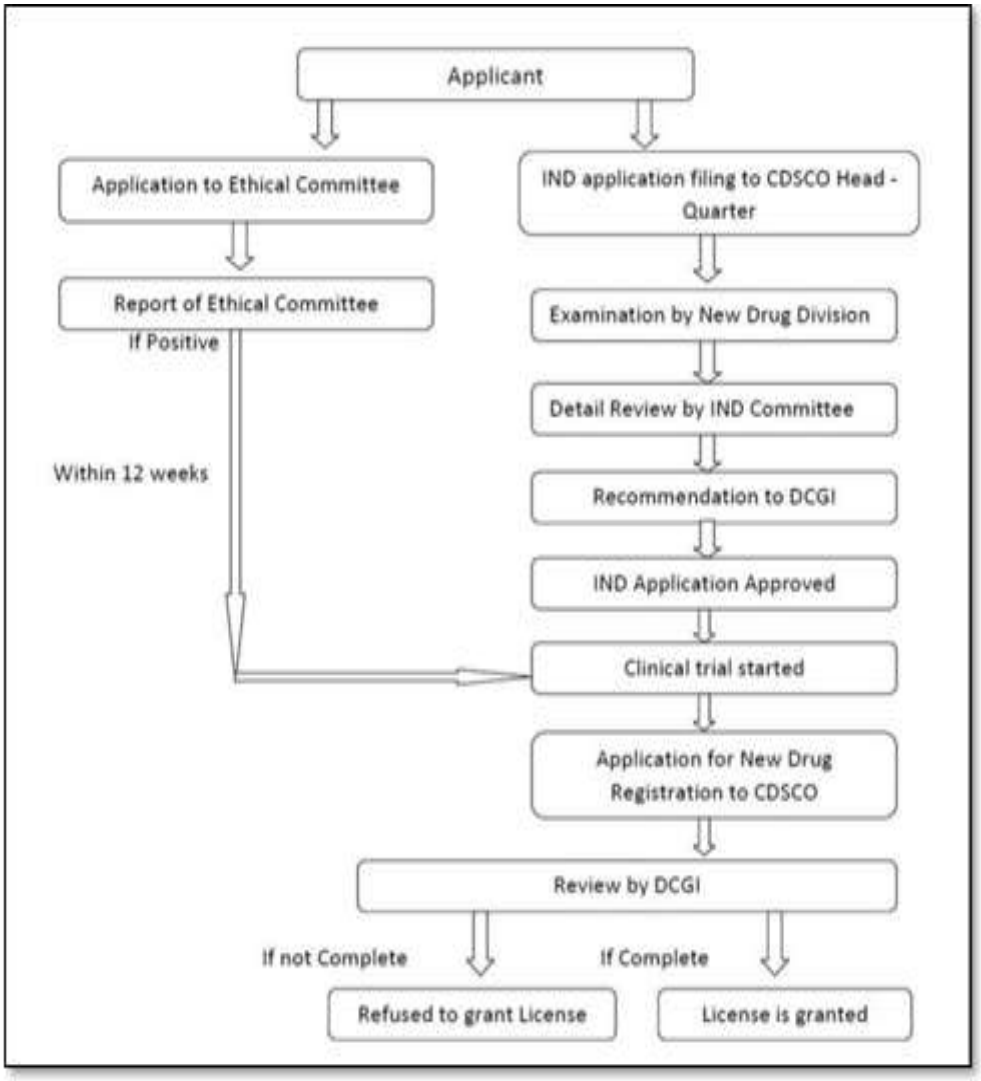

Fig.(2)FlowchartofdrugapprovalprocessinIndia.[24]

ThefollowingguidelinesmustbeadheredtounderThe DrugsandCosmeticsRulesof 1945:

- Rule122-A:Requestingauthorizationtoimportanewmedication
- Regulation122-B:requestforauthorizationtomanufactureanewdrugnotincludedin Schedule C and C1.
- Authorizationtoimport orproducefixeddosecombinationsisoutlined inRule 122-D.
- Rule 122-DA: Request forAuthorization to Perform Clinical Trials for Novel Drugs and Investigational New Drugs.
- DABRule122:PaymentforDeathorInjuryOccurringDuringClinicalTrials.[3]

The Drugs and Cosmetics Act has been amended to define Phase I–IV trials and to clearly outline the roles and responsibilities of sponsors and investigators. In 2006, the clinical trials were furthersplit into two groups. Clinical trials in othermarkets with capableand developed regulatoryframeworkscanbecarriedoutunderonecategory(categoryA),whiletheremaining ones fall under a different category (category B) Other thanA. Fast tracking is available for clinical trials of categoryA(approved in the United States, Great Britain, Switzerland, Australia, Canada, Germany, SouthAfrica, Japan, and the European Union), and approval is expectedtooccurineightweeksinIndia.CategoryBclin

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icaltrialsundergomorescrutinyand are approved in 16–18 weeks.[1]

Stagesofapproval:

1. SubmissionofClinicalTrialapplicationforevaluatingsafetyandefficacy.
2. Requirementsforpermissionofnewdrugsapproval.
3. Postapprovalchangesinbiologicalproducts: quality,safetyandefficacydocuments.
4. Preparationofthequalityinformationfordrug submissionfornewdrug approval.

Most countrieshaveadoptedtheCTDformat. Hence,CDSCOhas alsodecidedto adoptCTD formatfortechnicalrequirementsforregistrationofpharmaceuticalproductsforhumanuse.[1]

DRUGAPPROVALPROCESSINUSA:

The United States Food and Drug Administration (FDA) is responsible for regulating and overseeingawiderangeofproducts,includingfood,drugs,cosmetics,andmedicaldevicesfor both humans and animals. This regulatory oversight ensures that these products are safe, effective, and properly labelled for use by consumers. The FDA plays a crucial role in protecting public health and promoting innovation in these industries.[5]

THEEVALUATIONOFDRUGLAWANDREGULATIONINUS:[5-9]

1. The United States Pharmacopeia (USP) began in 1820 to create standards for the strength and purity of drugs. Over time, several key laws and regulations shaped drug oversight:
2. FoodandDrugsAct(1906):Thislawrequireddrugstomeetofficialstandardsfor strength and purity, marking an early step in regulating drug safety.
3. Federal Food, Drug and Cosmetic Act (1938): Enacted following the sulfanilamide tragedy,thislawmandatedthatdrugsmustbeprovensafebeforetheycouldbesold.It established the FDA's authority to oversee drug safety.
4. Kefauver-HarrisAmendment(1962):Passedafterthethalidomidedisaster,this amendment required drug manufacturers to demonstrate both safety and effectiveness before marketing a drug. It also mandated reporting of adverse effects to the FDA.
5. OrphanDrugAct(1983):Thislegislationincentivizeddrugcompaniestodevelop treatments for rare diseases by offering tax deductions and other benefits.
6. GenericDrugEnforcementAct(1992):Thislawaddressedissuesrelatedtotheapproval of generic drugs under the Abbreviated New Drug Application (ANDA) process, including penalties for false statements or information.
7. FDAModernizationAct (1997): This act brought changes to the Federal Food, Drug, andCosmeticAct,includingprovisionsforcollectingandassessinguserfeesfromdrug companiestoexpeditetheapprovalprocess.Italsointroducedmeasuresforaccelerated approval of certain drugs.

InvestigationalNewDrugApplication(INDA): [12]

ThedocumentyourefferringtoisanInvestigationalNewDrug(IND)application.Itprovides detailedinformationabouttheproduct'schemistry,manufacturing,pharmacology,toxicology, andanypreviushumanexperience.It'ssubmittedtotheFDAbeforehumantestingcanbegin, allowing the agency to review the safety and effectiveness data before clinical trials proceed.

TypesofIND:

1) AnInvestigatorIND:

AnInvestigatorINDissubmittedbyaphysicianwhobothinitiatesandconductsan investigation, and directly oversees the administration or dispensation of the investigational drug.ThistypeofINDistypicallyproposedbyaphysicianstostudyeitheranunapproveddrug or an approved product for a new indication or in a new patient population. It's a way for researchers to explore new uses or applications for drugs under investigation.

2) EmergencyUseIND:

This type of IND allows the FDAto authorize the use of an experimental drug in emergency situationswherethereisn'tenoughtimetosubmitastandardIND.Thiscan occurinsituations such as pandemics, natural disasters, or other public health emergencies where immediate access to investigational treatments is crucial.

3) TreatmentIND:

ATreatmentINDissubmittedforexperimentaldrugsthatshowpromiseinclinicaltestingfor serious or immediately life-threatening conditions. It allows patients with these conditions to accesstheexperimentaltreatmentwhilefinalclinicaltri

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alsareconductedandtheFDAreview takes place.This type of IND is used when the drug's benefits outweigh the risks, particularly for patients who have exhausted other treatment options.
The two main categories of INDs are commercial and research (non-commercial). An IND application must include information on animal pharmacology and toxicology studies, manufacturing details, and clinical trial protocols. Once submitted, the sponsor must wait 30 daysforFDAreviewbeforeinitiatinganyclinicaltrialsto ensurethesafetyofresearchsubjects.

INDContentandFormat:[6,13]

Certainly, here's the order in which the content and format of an Investigational New Drug (IND) applicationshouldbesubmitted,aspertherequirement soutlinedinthe21CodeofFederalRegulations (CFR),Section312.SubmittingtheINDapplicationint hisorderensuresthatallnecessaryinformation is provided systematically to the FDAfor review.

- FormFDA1571
- Tableofcontents
- Introductorystatementandinvestigationalplan
- Investigator'sbrochure
- Protocols
- Chemistry,manufacturingandcontrol(CMC)inf ormation
- Pharmacologyandtoxicologyinformation
- Previoushumanexperience
- Additionalinformation

NewDrugApplication(NDA):
ANew DrugApplication (NDA) is submitted to the FDAto obtain approval for marketing a new drug in the USA. An NDA includes all the information provided in the Investigational NewDrug(IND)application,alongwiththeresultsofcli nicalstudiesdemonstratingthesafety andefficacyofthedrug.OnceanNDAissubmitted,theF DAbeginsthereviewprocesswithin 60days.Duringthisreview,theFDAevaluatesthedatap rovidedtoensurethatthedrugissafe and effective for its intended use.This process involves thorough examination of clinical trial results,manufacturingprocesses,labeling,andotherre levantinformationtomakeaninformed decision about whether to approve the drug for marketing in the USA.

ContentsandFormatofNDA[6]**:**
Twocopiesoftheapplication are:

1. ArchivalCopy;
2. ReviewCopy

(1) Archivalcopy:

The Archival Copy of the New Drug Application (NDA) indeed serves as a vital reference source for FDA reviewers, containing detailed information that might not be present in the review copy. It also includes copies of tabulations and clinical study case report forms. This comprehensivedocumentensuresthatFDAreviewers haveaccesstoallnecessaryinformation to conduct a thorough evaluation of the NDA and make informed decisions regarding drug approval.

Itcontainsthefollowing elements:

- ApplicationformFDA356
- Index
- Summary
- Technicalsections:Furthertypedto

1. Chemistry,manufacturingandcontrolssection
2. Non-clinicalpharmacologyandtoxicologysection
3. Humanpharmacokineticsandbioavailabilitysec tion
4. Microbiologysection
5. Clinicaldata section
6. Statisticalsection
7. Pediatricuse section

- Samplesandlabelling
- Casereportforms

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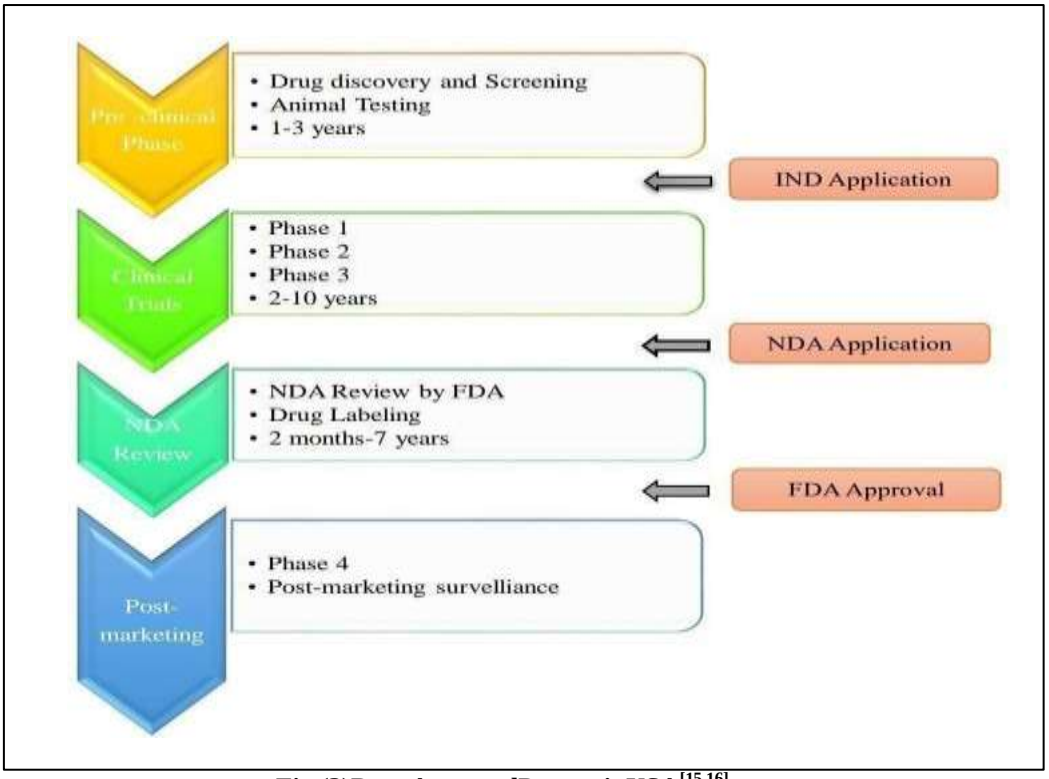

Fig.(3)DrugApprovalProcessinUSA[15,16]

2)ReviewCopy:
Each technical section is separately bound in each folder. r. Each technical section should contain:

- Index
- CopyofFDAForm 356h
- Copyofcover letter
- Lettersofauthorization
- Copyofapplicationsummary

TheFDAtypicallyholdstwomeetingswiththesponsor duringthedrugdevelopmentprocess: one after Phase 2 clinical trials and another before the submission of a New DrugApplication (NDA), known as a pre-NDAmeeting. During these meetings, the review team evaluates the study results and decides whether to approve the application.

AbbreviatedNewDrugApplication(ANDA):[12]

AnAbbreviatedNewDrugApplication(AN DA)issubmittedforproductscontainingthesame or closely related active ingredients, dosage form, strength, route of administration, use, and labellingasapreviouslyapprovedproductthathasbeen demonstratedtobesafeandeffective. Typically used for generic drugs after the patent for the original product has expired,ANDAs must meet bioequivalence and pharmaceutical equivalence standards. The submission is reviewedandapprovedbythecenterforDrugEvaluatio nandResearch,specificallytheOffice of Generic Drugs.

ContentandFormatofANDA:[6]

- Applicationform
- Tableofcontents
- BasisforANDAsubmission
- Conditionsofuse
- Activeingredients
- Routeofadministration,dosagefrom,strength
- Bioequivalence
- Labelling
- Chemistry,manufacturingandcontrol
- Humanpharmacokineticsand bioavailability
- Samples
- Analyticalmethods
- Casereportformsandtabulations.

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TheDivisionofBioequivalence'sOfficeofGenericDrugswithinCDERissuedthe"Guidance on Statistical Procedures for Bioequivalence Studies Using a Standard Two Treatment Crossover Design" in July 1992. This guidance outlines regulations for conducting valid statistical analyses for assessing bioequivalence, ensuring the accuracy and reliability of such assessments.Additionally, the FDAhas released a draft guidance titled "In Vivo
Bioequivalence Studies Based on Population and Bioequivalence," which offers recommendations to sponsors of Investigational New Drug Applications (INDs), New Drug Applications(NDAs),andAbbreviatedNewDrugApplications(ANDAs)whoplantoconduct studies comparing pharmacokinetic metrics. These guidance documents serve to standardize procedures and uphold rigorous standards in bioequivalence assessment within the pharmaceutical industry.

TheFDAmaintainsacomprehensivelistofall approveddrugproducts,includingbothbranded and generic drugs, in the "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as the Orange Book. This resource serves as a valuable reference for healthcare professionals, researchers, and the public, providing information on thetherapeuticequivalenceofvariousdrugproducts.It categorizesdrugsbasedontheiractive ingredientsandevaluatestheirtherapeuticequivalence,facilitatinginformeddecision-making regarding drug selection and substitution.

SupplementalNewDrugApplication(SNDA):[6]
After approval of NDA orANDA, all significant changes in the conditions described in the applicationsmustbeapproved,byfilingasupplemental NDAorANDA.Suchchangesshould approveCDER.

DRUGAPPROVALPROCESSIN EUROPE:[21-23]
In the European Union, drugs must go through two regulatory steps before they can be marketed:

1. ClinicalTrialApplication(CTA):Approvalfortesting onhumansineachmemberstate.
2. MarketingAuthorizationApplication(MAA):Approvalformarketingeitheratthe national or centralized level.

Thissystemensuresdrugsmeethighstandardsandallowstimelyaccesstotreatments.

There are 28 member states in the European Union (as of July, 2013); Clinical Trial Applications are approved at the member state level, whereas marketing authorization applications are approved at both the member state and centralized levels.

Centralizedprocedure:
Indeed,thecentralizedprocedureintheEuropeanUnionisdesignedtostreamlinetheapproval process for drugs, allowing applicants to obtain a marketing authorization that is valid throughout the EU, as well as in Norway, Iceland, and Liechtenstein. Key points about the centralized procedure include:

Single Authorization: It results in a single authorization that is recognized across all EU member states, as well as in Norway, Iceland, and Liechtenstein.

Evaluation Process: The application is evaluated by an assigned Rapporteur, who is typically anexpertfromoneoftheEUmemberstates.Theevaluationalsoinvolvesinputfromother EU member states.

Timeline: The European MedicinesAgency (EMA) aims to issue an opinion within 210 days ofthesubmission oftheapplication.AftertheEMA's opinion is issued, it is thensubmittedto the European Commission for final approval.

Overall, the centralized procedure expedites the approval process for drugs intended to treat seriousdiseasesorconditions,ensuringtimelyaccesstonewtreatmentsforpatientsacrossthe EU and associated countries.

The centralized procedure is mandatory for certain categories of medicines in the European Union. These include:

- **Biotechnology-derived Medicines:** Drugs derived from biotechnological processes, such as genetic engineering
- **Medicines for Serious Diseases:**Drugs intended for the treatment of serious diseases such as Cancer, HIV/AIDS, diabetes, neurodegenerative disorders, autoimmune diseases, and other immune dysfunctions.
- **Orphan Medicines:**Medicines designated as 'Orphan medicines,' which are used for rarediseases.Thesareconditionsthataffectasmallnumberofpeopleintheeu,often referred to as orphan diseases because they do not attract significant research and development efforts by pharmaceutical companies due to their rarity.

Forthesecategoriesofmedicines,thecentralizedproce

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dureensuresaharmonizedand
efficient regulatory process, facilitating timely access to treatments for patients across the EU and associated countries.

MutualRecognitionProcedure:

The Mutual Recognition Procedure (MRP) is another regulatory pathway available in the European Union for obtaining marketing authorization for medicinal products. In the MRP:

One member state, known as the Reference Member State (RMS), reviews the marketing authorization application. After approval by the RMS, the applicant can then submit the application to other member states, known as Concerned Member States (CMS), for recognition.TheCMScaneitheragreetorecognizethe marketingauthorizationgrantedbythe RMS or raise objectionsif there are specific concerns regarding the product's safety, efficacy, or quality. If there are no objections or if objections are resolved satisfactorily, the product receives marketing authorization in the CMS. This procedure allows for the efficient authorization of medicinal products across multiple EU member states by leveraging the assessment performed by the RMS, while still allowing individual member states to address specific concerns if necessary.

- IntheMutualRecognitionProcedure(MRP)ofthe EU,theapplicantsubmitsthesame dossier to all member states where they seek marketing authorization. This ensures consistencyinevaluationacrossjurisdictionsands treamlinestheauthorization process.
- IntheMutualRecognitionProcedure(MRP),once onememberstatedecidestoevaluate themedicinalproductandbecomestheReference MemberState(RMS),itnotifiesthis decision to the other member states to whom applications have also been submitted. These other member states then become the Concerned Member States (CMS) in the procedure.Thisnotificationinitiatestheprocessof mutualrecognition,wheretheRMS evaluates the product and shares its findings with the CMS for their consideration in granting marketing authorization.

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 may process takes 390 days.

Decentralizedprocedure:

In the Mutual Recognition Procedure (MRP), companies can simultaneously apply for authorization in multiple EU countries for products that have not yet been authorized in any EUcountryanddonotqualifyforthecentralizedproced ure.OncetheReferenceMemberState (RMS)completesitsassessmentandpreparestheassess mentreport,anycommentsorconcerns from the Concerned Member States (CMS) are taken into account. However, ultimately, marketing authorization is granted according to the decision made by both the RMS and the CMS involved in the procedure. This decentralized approach allows for a coordinated evaluation process among multiple EU member states, ensuring that products meet the necessary standards for safety, efficacy, and quality before being granted marketing authorization.

- Generally used for those products that has not yet received any authoriation in an EU country.
- Time:210days.

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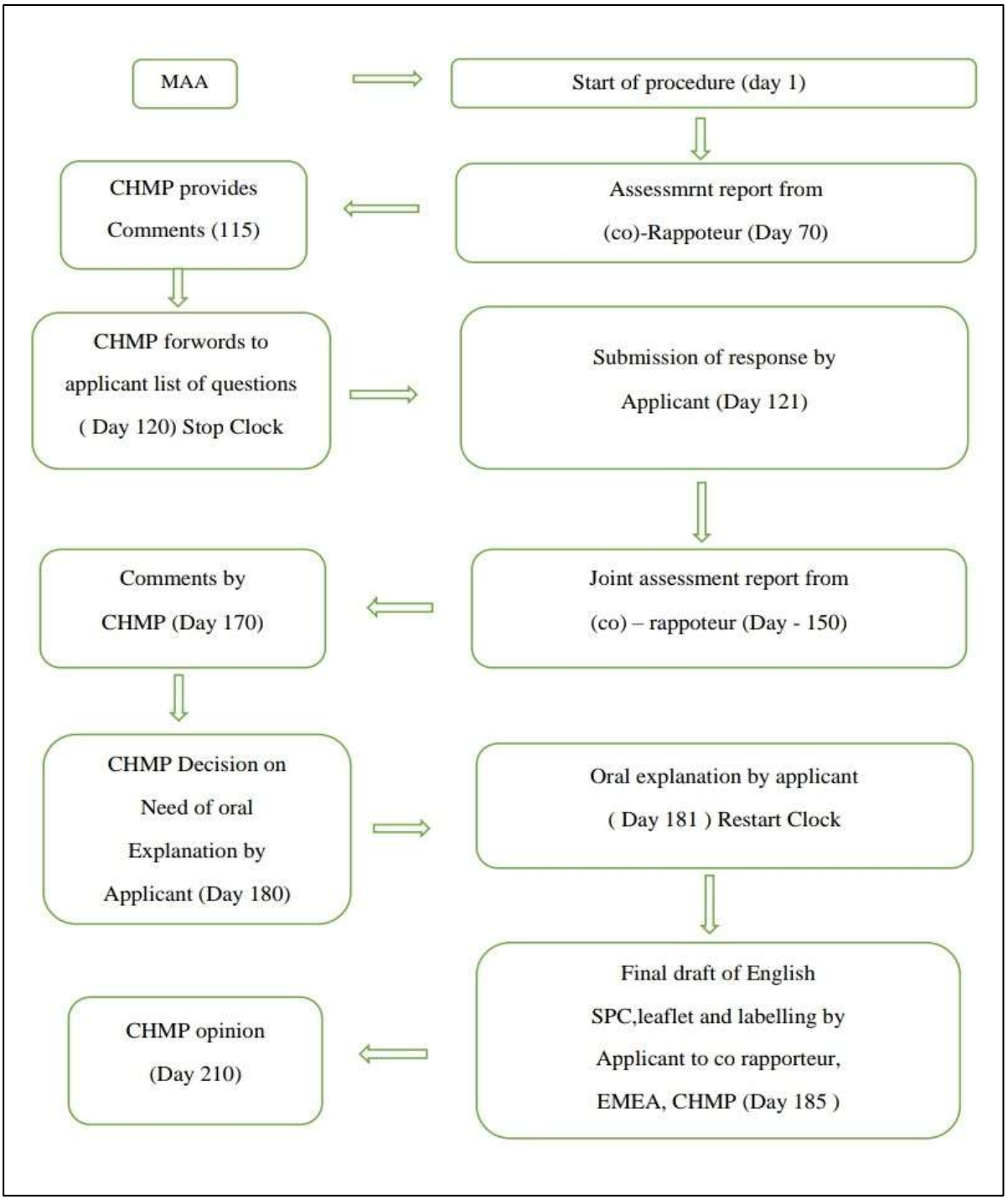

Fig(4):Flowchartofcentralizedprocedure

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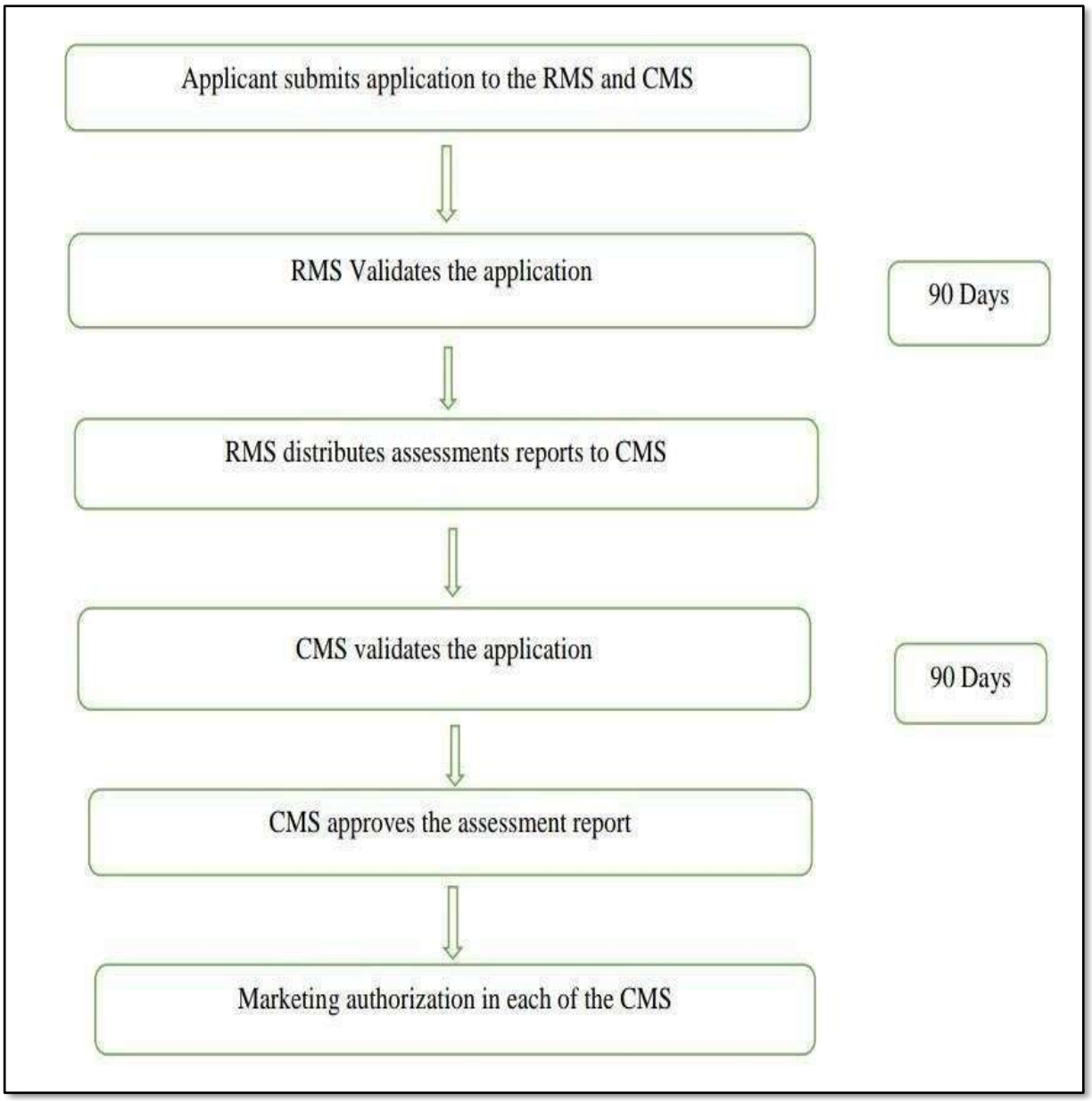

Fig.(5):FlowChartofMRP

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