REGULATORY AFFAIRS (MPH104T)

Non clinical drug development: Global submission of IND (Investigational New Drug), NDA (New drug application), ANDA (abbreviated new drug application), Investigation of medicinal products dossier (IMPD) and investigator brochure (IB).

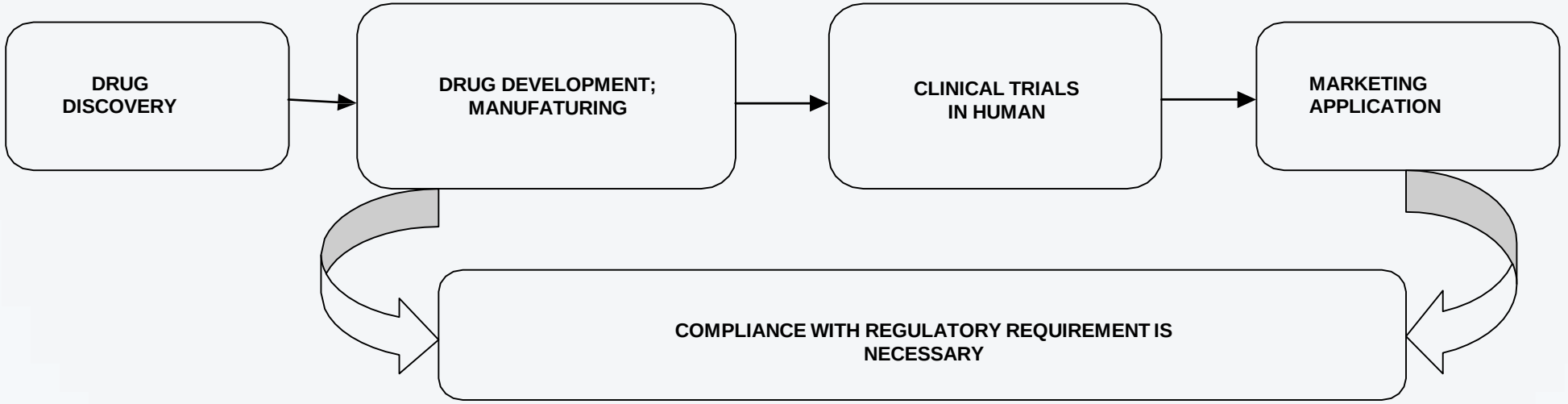
Manas Bhowmik

Department of Pharmaceutical Technology

Global regulatory requirements

Pharmaceutical Technology

- Different countries have different regulatory requirements for approval of new drug
- For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task
- Required necessary knowledge about regulatory requirement for MAA of each country
- The basic regulation is understand from the following flowchart:



New drug application (NDA)

Pharmaceutical Technology

- New drug application (NDA) is an application submitted to the respective regulatory authority for permission to market a new drug.
- To obtain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing procedures.

Different Phases of clinical trials:

- Pre clinical study - Mice, Rat, Rabbit, Monkeys
- Phase I - Human pharmacology trial (1-3 years, Human~100) - estimation of safety , tolerability and Pharmacokinetics
- Phase II - Exploratory trial (2 years, Human~300) - estimation of effectiveness (dose) and broad efficacy, short term side effects and additional safety
- Phase III - Confirmatory trial (3-4 years, Human~ up to 3000) - Confirmation of therapeutic benefits, safety and effectiveness of drug from data of different populations, dosages and its combination with other drugs
- Phase IV - Post marketing trial - Studies done after drug approval

New drug application (NDA)

Pharmaceutical Technology

After NDA received by the agency:

Technical screening to ensure sufficient data and information submitted in each area for justifying "filing" the application.

After review of an NDA, there are 3 possible actions that can send to sponsor (applicant):

1. Not approvable- in this letter list of deficiencies and explain the reason.
2. Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies.
3. Approval- it state that the drug is approved.

If the action taken is either an approvable or a not approvable, then the regulatory body provides applicant with an opportunity to meet with agency and discuss the deficiencies

DRUG APPROVAL PROCESS IN US

Pharmaceutical Technology

- In 1820, the new era of USA drug regulation was started with the establishment of U.S. Pharmacopoeia
- In 1906, Congress passed the original Food and Drugs Act, which require that drugs must meet official standards of strength and purity
- In1937, due to sulphanilamide tragedy (diethylne glycol as solvent which is poisonous and cause kidney damage)
- The Federal Food, Drug and Cosmetic Act (of 1938) was enacted and added new provisions that new drugs must be shown safe before marketing
- In1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective (for the claims made in labeling)
- The United States has perhaps the world's most stringent standards for approving new drugs
- The Food and Drug Administration (FDA) is responsible for protecting and promoting public health. FDA's new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug application (NDA) approval. FDA approval process begins only after submission of investigational new drug (IND) application.

Investigational New Drug (IND) Application

Pharmaceutical Technology

✓An application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials

✓The IND application should provide high quality preclinical data to justify the testing of the drug in humans

✓Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. A firm or institution, called a Sponsor, is responsible for submitting the IND application

A pre - IND meeting can be arranged with the FDA to discuss a number of issues:

•The design of animal research, which is required to lend support to the clinical studies

•The intended protocol for conducting the clinical trial

•The chemistry, manufacturing, and control of the investigational drug.

Such a meeting will help the Sponsor to organize animal research, gather data, and design the clinical protocol based on suggestions by the FDA.

Next step is clinical trials

New drug application (NDA)

Pharmaceutical Technology

❑A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labeling.

❑The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Centre for Drug Evaluation and Research by a team of scientists.

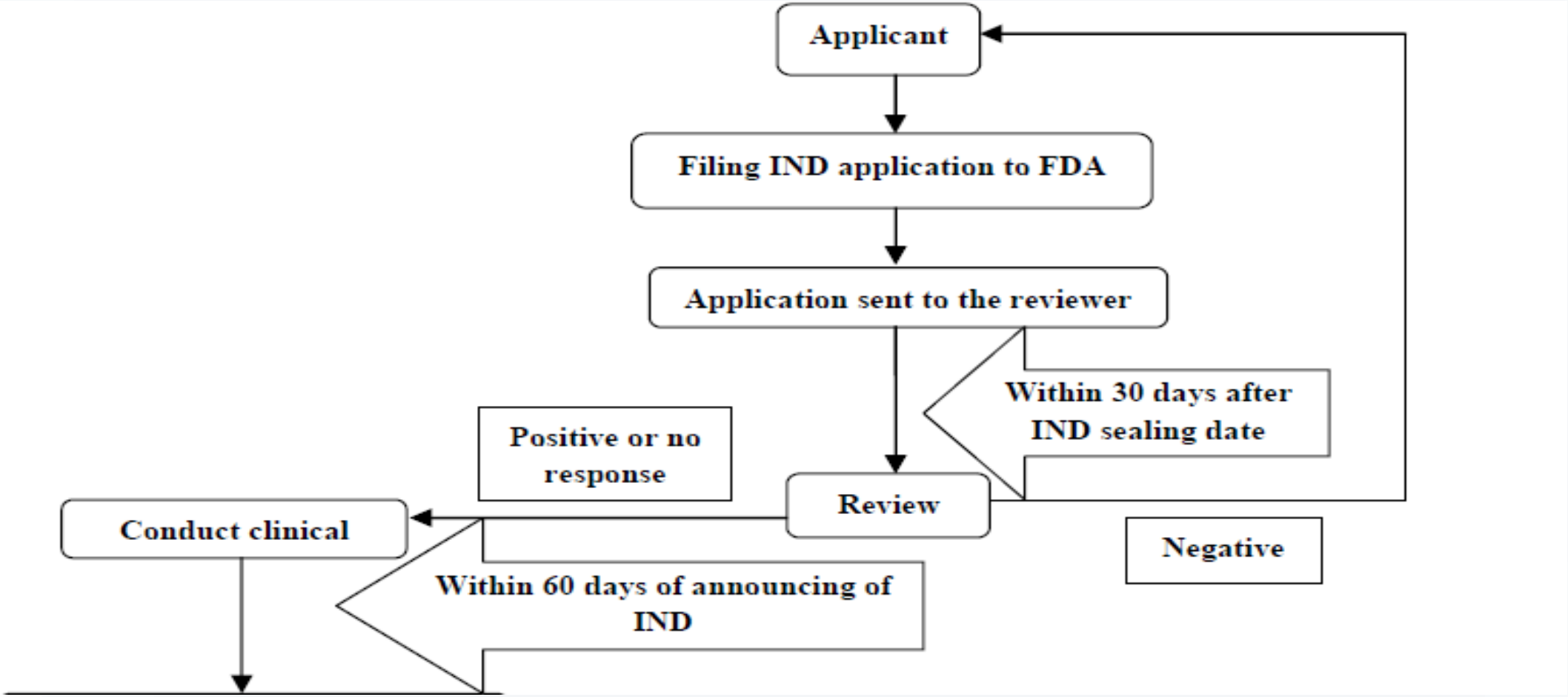
❑If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and sell the drug in the United States

❖Approval of an NDA is granted within two years (on an average)

❖The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored

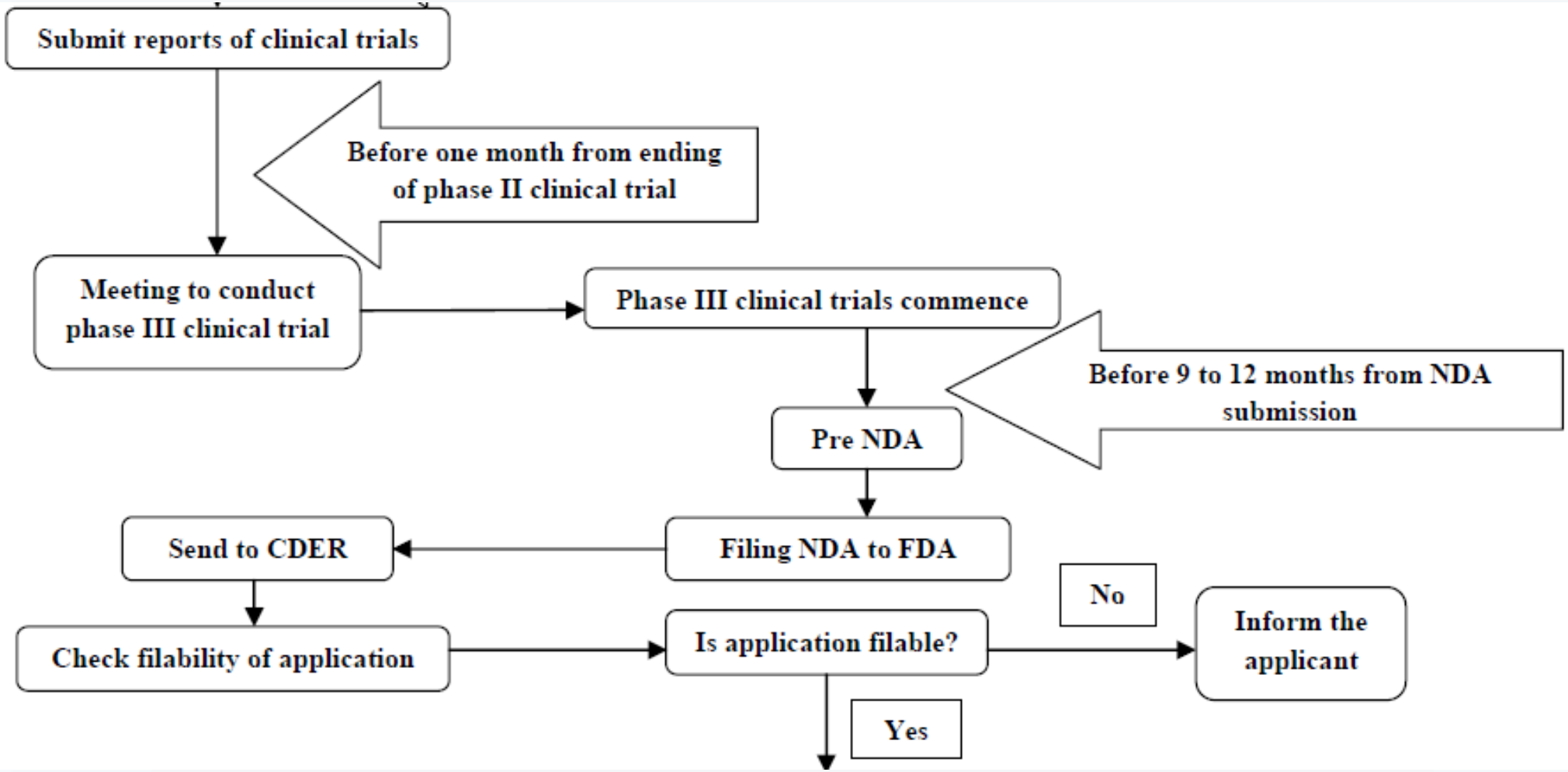
Drug approval process in USA & Clinical Trial for EU

Pharmaceutical Technology



Drug approval process in USA & Clinical Trial for EU

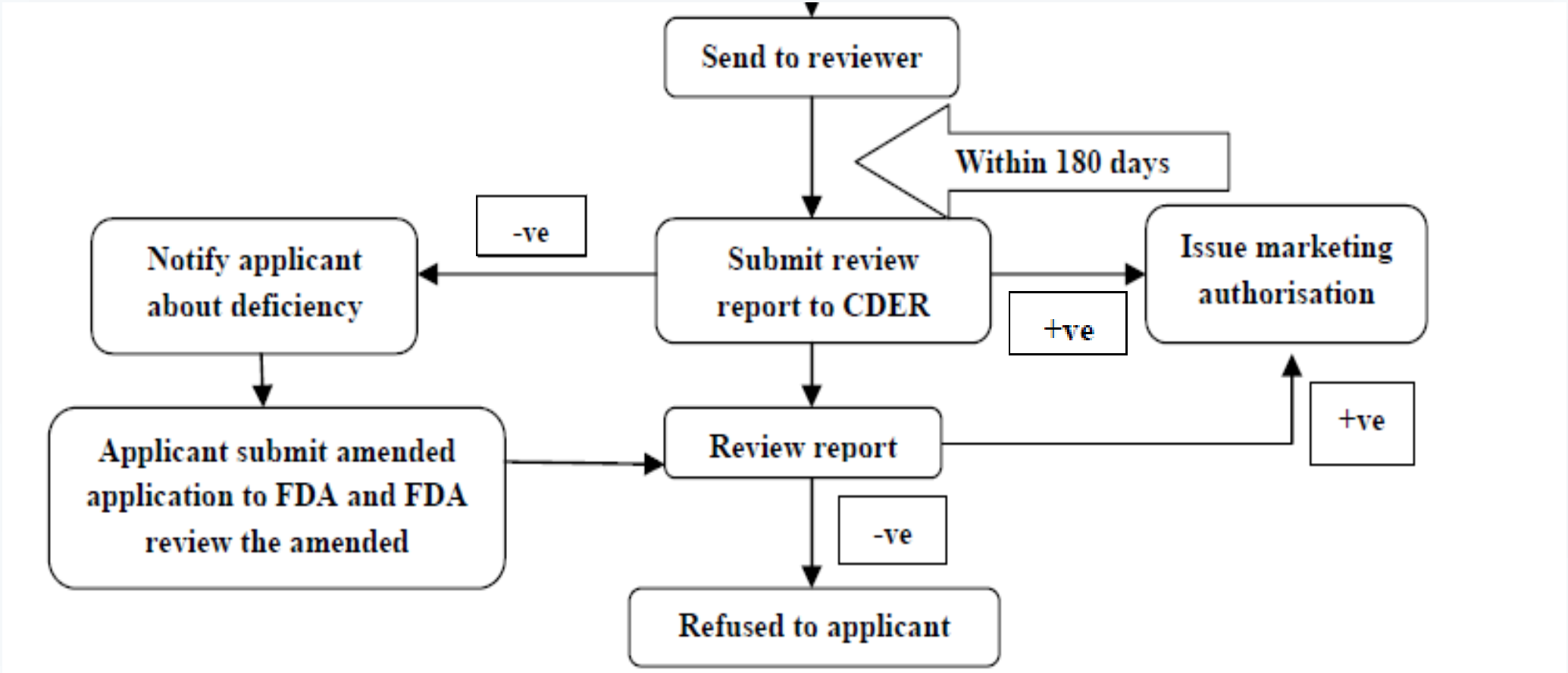
Pharmaceutical Technology



The Center for Drug Evaluation and Research (CDER) performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States

Drug approval process in USA

Pharmaceutical Technology



Drug approval process in EU

Pharmaceutical Technology

- In European union (EU), the medical products are approved for marketing at the National level initially
- The mutual recognition procedure was introduced in 1938 and a single national review in case of pharmaceutical/medicinal product for marketing authorization in EU's countries was made feasible
- The primary aim of this procedure was to create a united standard for product review among national regulatory authorities
- In 1987, for high-technology or biologically derived products, the concertation procedure was established by directive 87/22, in which product assessment should be completed by Committee for Proprietary Medicinal Products (CPMP) besides the normal national regulatory review
- In 1993, by The European council regulation (EEC) 2309/93, the concertation procedure was replaced with centralized procedure, by which all the high-tech and biologically derived product was reviewed and granted EU's wide marketing authorization by the EU's CPMP.
- The drug approval process in European countries is also accomplished in two phases: clinical trial and marketing authorization

Drug approval process in EU

Pharmaceutical Technology

- A clinical trial application (CTA) is filed to the competent authority of the state to conduct the clinical trial within EU
- The competent authority of that member state evaluates the application
- The clinical trials are conducted only after the approval
- The purpose and phases of clinical trials are similar as specified in FDA drug approval process
- After completing of all three phases of clinical trial, marketing authorization application (MAA) is filed including all animal and human data, its analyses, as well as pharmacokinetics, manufacturing and proposed labeling
- In the EU's countries, the company have a choice of following regulatory Centralized Procedure, Decentralized Procedure, Nationalized Procedure or Mutual Recognition Procedure

Regulatory Centralized Procedure (EU)

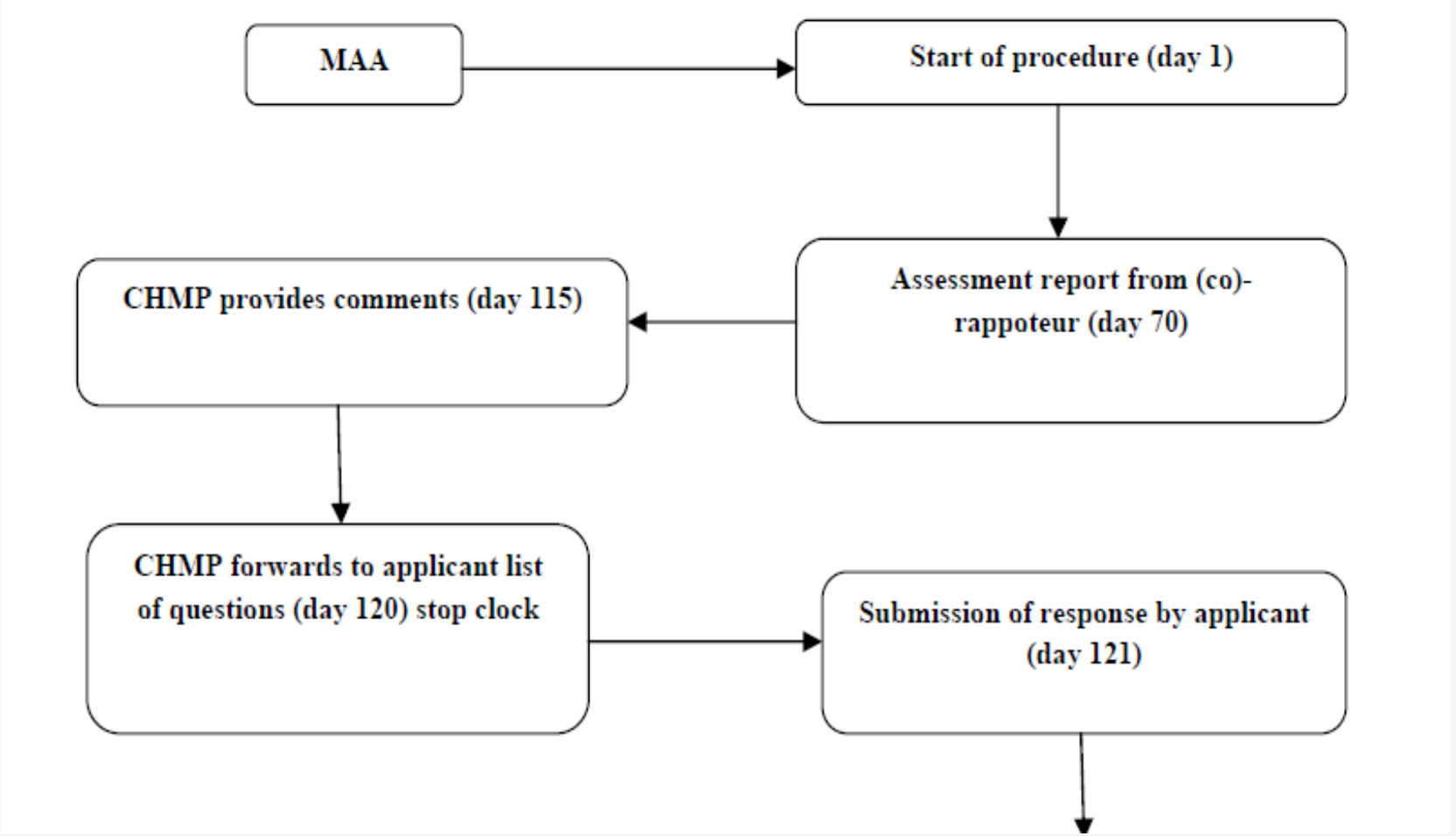
Pharmaceutical Technology

- The Committee for Human Medicinal Products (CHMP) evaluate the applications received by the EMEA (Europe, Middle East, and Africa)
- In view of the applicant's preference, CHMP contracts out assessment work in one of the member states (the "rapporteur“)
- After the complete assessment, the CHMP deliver opinion to EU Commission within 210 days
- The EU Commission requests comments from other member states, if a positive opinion from CHMP is received
- The other member states can respond in about 28 days
- When a license is recommended, a European Public Assessment Report (EPAR) is produced and marketing authorization is issued and this authorization is valid throughout the European Union for five years, however, the extension can be applied to the EMEA three months before the expiration of this period.

Centralized process is compulsory for (i) medicines which are derived from any biotechnology processes, such as genetic engineering (ii) medicines which are intended for the treatment of Cancer, HIV/AIDS, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions (iii) Orphan medicines (medicines used for rare diseases)

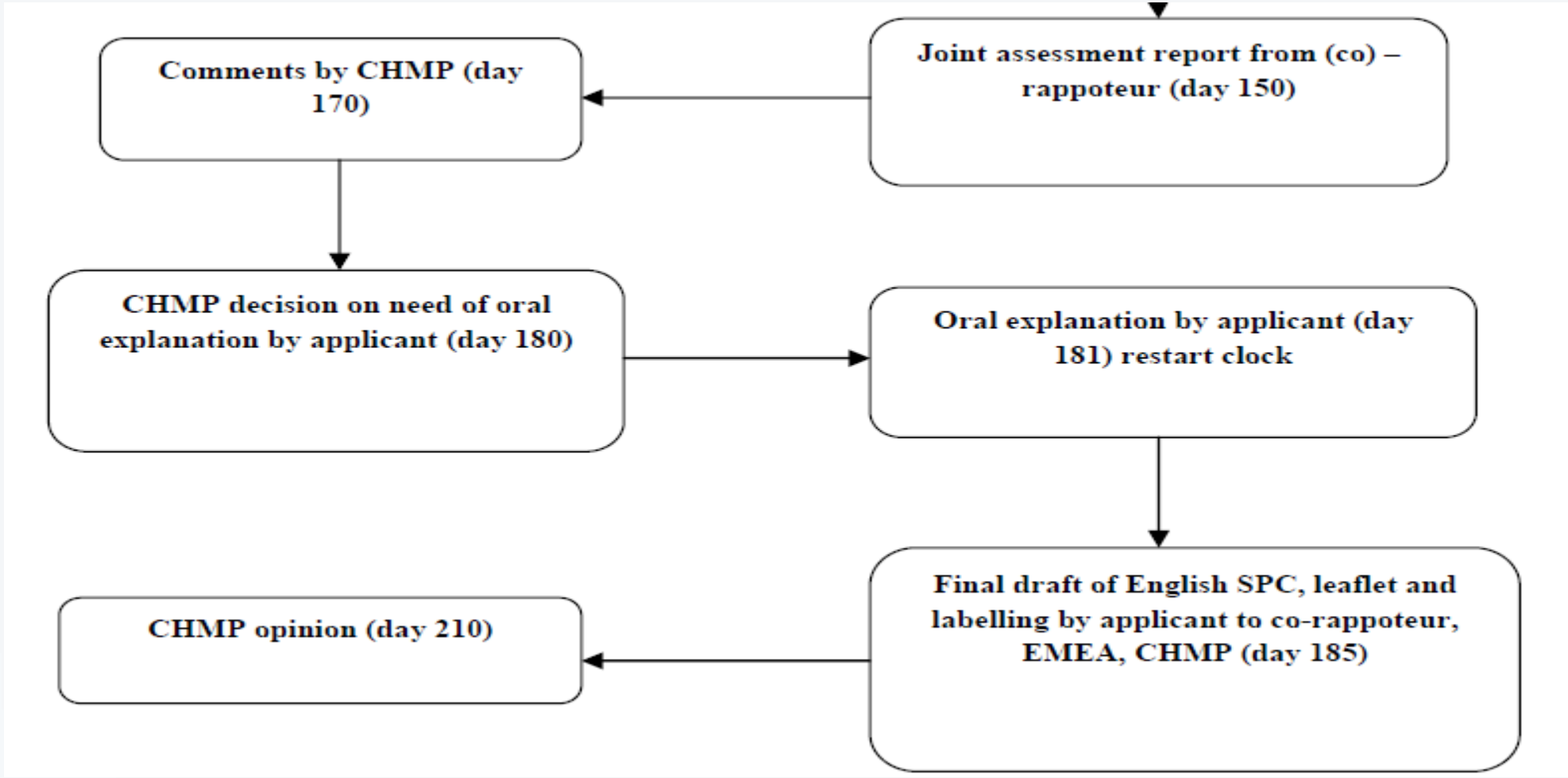
Regulatory Centralized Procedure (EU)

Pharmaceutical Technology



Regulatory Centralized Procedure (EU)

Pharmaceutical Technology



EMEA (Europe, Middle East, and Africa); SPC (Supplementary Protection Certificate)

Regulatory Decentralized Procedure (EU)

Pharmaceutical Technology

▪In order to obtain marketing authorizations in several member states, the centralized procedure is not mandatory; in such case the decentralized procedure is to be used.

•An application is submitted to competent authorities of each of the member states, where a marketing authorization is to be sought

•The information like quality, efficacy, safety, administrative information shall be submitted and a list of all Concerned Member States (CMSs) and one member state to act as Reference Member State (RMS)

•A draft assessment report on the medicinal product is prepared and the CMSs and the RMS validate the application within a time frame of 14 days

•The RMS prepare draft summary of product characteristics, labeling and package leaflet within 120 days

•This report can be approved within 90 days

•If a medicinal product is supposed to cause potential serious risk to public health, CMS(s) will inform to other CMS, RMS and applicant and further decision in this regard is taken within 30 days

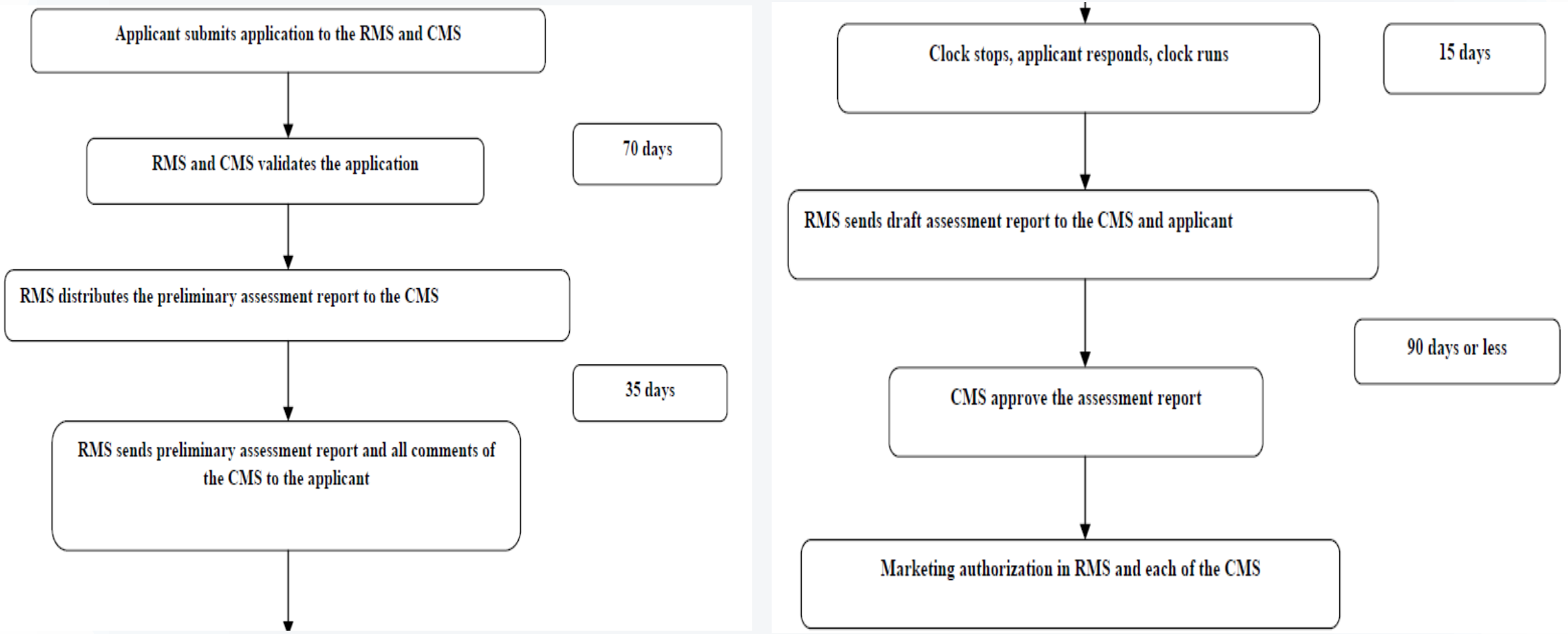
Regulatory Decentralized Procedure (EU)

Pharmaceutical Technology

- Within 60 days of the communication of the points of disagreement, all member states reach to an agreement on the action to be taken
- After reaching to an agreement of the member states, the RMS records the agreement and informs to the applicant
- If the member states could not reach an agreement, then CHMP intervenes and take a final decision keeping in view of the written or oral explanations of the applicant

Regulatory Decentralized Procedure (EU)

Pharmaceutical Technology



Concerned Member States (CMS), Reference Member State (RMS)

Regulatory Nationalized Procedure (EU)

Pharmaceutical Technology

- 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

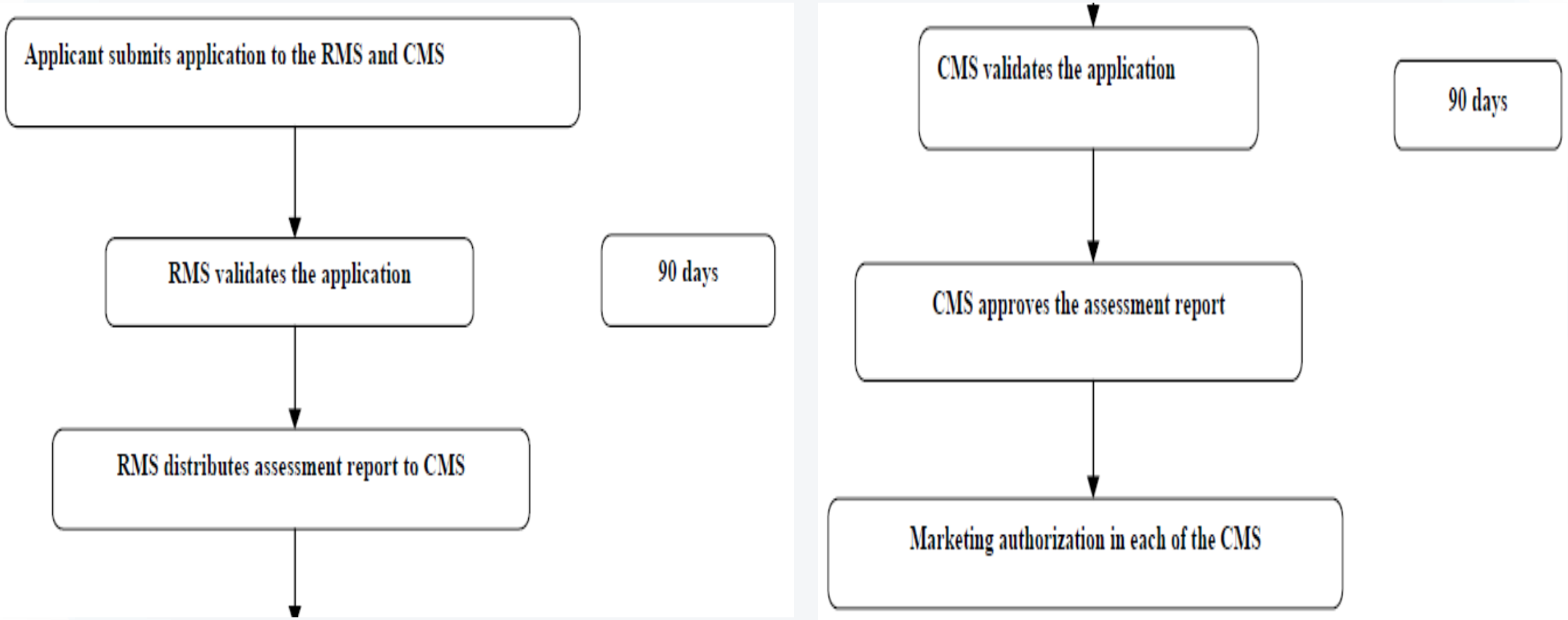
Regulatory Mutual Recognition Procedure (EU)

Pharmaceutical Technology

- 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

Regulatory Mutual Recognition Procedure (EU)

Pharmaceutical Technology



Drug approval process in India

Pharmaceutical Technology

•The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics

•The Central Drugs Standard Control Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] were established

•In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945

•Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure

•When a company in India wants to manufacture/ import a new drug it has to apply to from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945

•In order to prove its efficacy and safety in Indian population it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format

•Rule- 122A of the Drug and Cosmetics Act says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries

Drug approval process in India

Pharmaceutical Technology

•Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required

•Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials

•Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central Drugs Standard Control Organization (CDSCO)

•The regulations under Drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing

Drug approval process in India

Pharmaceutical Technology

•The changes in the Drugs And Cosmetics Act includes, establishing definitions for Phase I-IV trials and clear responsibilities for investigators and sponsors

•The clinical trials were further divided into two categories in 2006; one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) other than A

•Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks

•The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks

• An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI

•The date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached

•A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee

Drug approval process in India

Pharmaceutical Technology

•To determine the maximum tolerated dose in humans, adverse reactions, etc. on healthy human volunteers, Phase I clinical trials are conducted

•The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level

•The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims

•Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centres, if the new drug substance is not marketed in any other country.

• The new drug registration (using form 44 along with full pre-clinical and clinical testing information) is applied after the completion of clinical trials

•The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy

•The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted

Drug approval process in India

Pharmaceutical Technology

•The application can be reviewed in a range of about 12-18 months

•After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials, in which new uses or new populations, long-term effects, etc. are explored

• Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States.

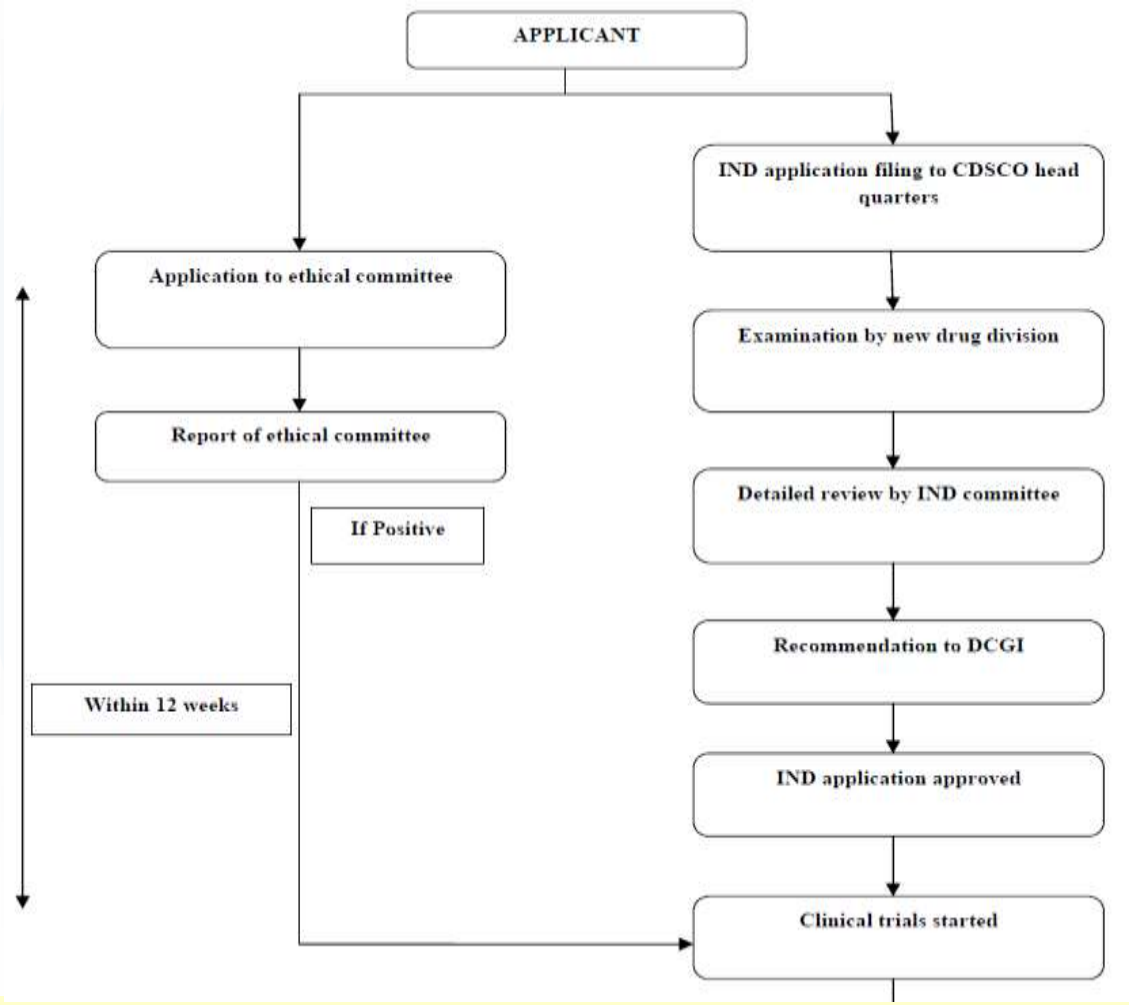
• Most countries have adopted the CTD format; CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use

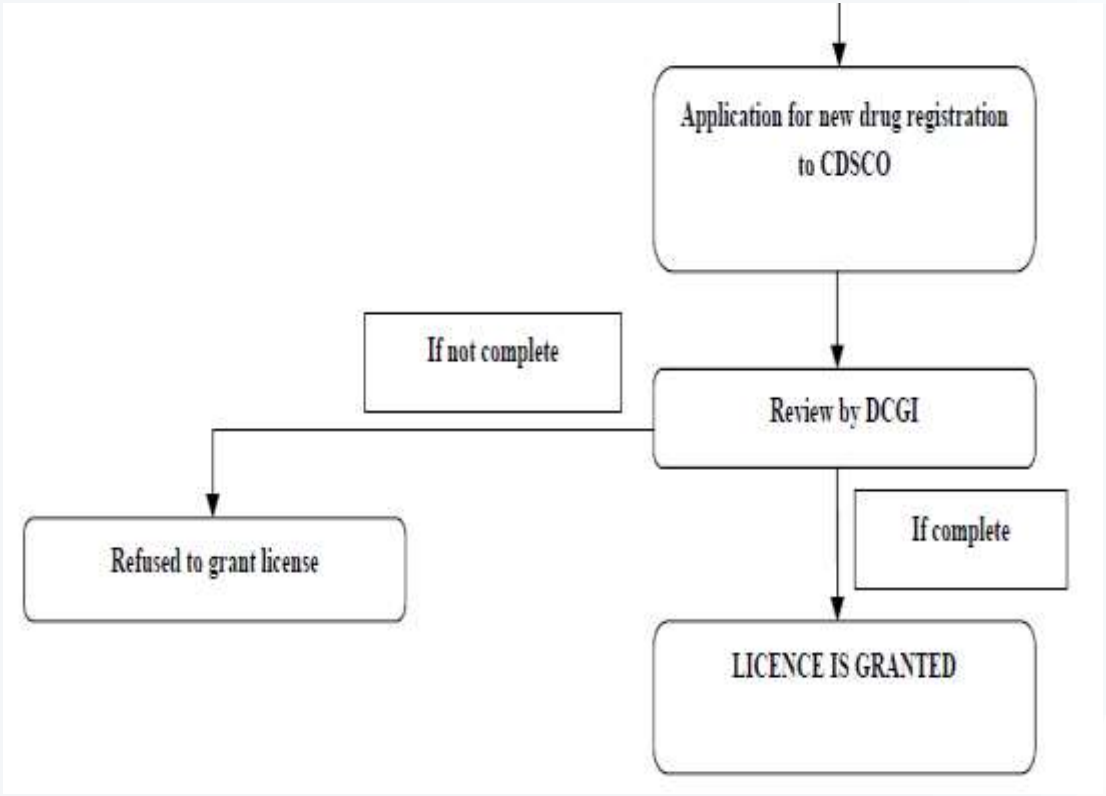
Stages of approval:

1. Submission of Clinical Trial application for evaluating safety and efficacy
2. Requirements for permission of new drugs approval
3. Post approval changes in biological products: quality, safety and efficacy documents
4. Preparation of the quality information for drug submission for new drug approval

Drug approval process in India

Pharmaceutical Technology





Regulatory difference (US, EU, India)

Pharmaceutical Technology

REQUIREMENTS	US	EU	INDIA
Agency	One agency USFDA	Multiple agencies • EMEA • CHMP • National health agencies	One agency DCGI
Registration process	One registration process	Multiple registration process • Centralized (European community) • Decentralized (at least 2 member states) • Mutual recognition (at least 2 member states) • National (1 member state)	One registration process
TSE/BSE study data	Not required	Required	Required
Braille code	Braille code is not required on labeling	Braille code is required on labeling	Braille code is not required on labeling
Post approval changes	Post approval changes in the approved drug: • Minor • Moderate • major	Post variation in the approved drug: • Type IA • Type IB • Type II	Post approval changes: • Major • Moderate

Difference in administrative requirements (US, EU, India)

Pharmaceutical Technology

REQUIREMENTS	US	EU	INDIA
Application	ANDA/NDA	MAA	MAA
Debarment classification	Required	Not required	Not required
Number of copies	3	1	1
Approval timeline	18 months	12 months	2 - 18 months
Fees	Under $2 million – NDA application $1,520 – ANDA application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS:£99,507	50,000 INR
Presentation	eCTD and paper	eCTD	Paper

Manufacturing and control requirements (US, EU, India)

Pharmaceutical Technology

REQUIREMENTS	US	EUROPE	INDIA
Number of batches	1	3	1
Packaging	A minimum of 1,00,0000	Not required	Not addressed
Process validation	Not required at the time of submission	Required	Required
Batch size	1 pilot scale or minimum of 1 lakh units whichever is higher	2 pilot scale plus 1 lab batch or minimum of 1 lakh units whichever is higher	Pilot scale batch

Regulatory overview

Pharmaceutical Technology

The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory task such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some counties all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralized and State authorities. Some counties have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like as in USA, EU, and Japan , it is mandatory that the dossier

Regulatory overview

Pharmaceutical Technology

Generally, the drug approval process comprised mainly the two steps, application to conduct **clinical trial** and application to the regulatory authority for **marketing authorization** of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects. In most of the counties, sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time, fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States. India also follows the same.

Regulatory overview

Pharmaceutical Technology

ICH Guidelines will ultimately reduce the need to duplicate work carried out during the research and development of new drugs. Therefore, harmonization of drug approval processes either by ICH or WHO may be initiated at global level.

The regulatory agency for US and India is a single agency i.e. USFDA and CDSCO respectively, whereas in EUROPE, there are three regulatory agencies, they are EMEA, CHMP and NATIONAL HEALTH AGENCY.

Europe also has multiple regulatory procedures when compared to US and India. The approval time in all the countries is almost the same i.e., 12 to 18 months. The fee for the new drug approval in US is very high when compared to Europe and India.

The Drug approvals in the US, Europe & India are the most demanding in the world. The primary purpose of the rules governing medicinal products in US, Europe & India is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

Investigation of medicinal products dossier (IMPD)

Pharmaceutical Technology

The table of contents for a full IMPD follows the headings as given by the relevant guidelines. The IMPD headings are based on the assumption that detailed information will be provided by the Investigational Brochure. Only relevant information will have to be provided and several headings can in general remain empty.

2.1.S	DRUG SUBSTANCE
2.1.S.1	General Information
2.1.S.1.1	Nomenclature
2.1.S.1.2	Structure
2.1.S.1.3	General Properties
2.1.S.2	Manufacture:
2.1.S.2.1	Manufacturer(s)
2.1.S.2.2	Description of Manufacturing Process and Process
2.1.S.2.3	Control of Materials
2.1.S.2.4	Controls of Critical Steps and Intermediates
2.1.S.2.5	Process validation and/or Evaluation
2.1.S.2.6	Manufacturing Process Development

Investigation of medicinal products dossier (IMPD)

Pharmaceutical Technology

2.1.S.3	Characterisation:
2.1.S.3.1	Elucidation of Structure and Other Characteristics
2.1.S.3.2	Impurities
2.1.S.4	Control of Drug Substance:
2.1.S.4.1	Specification
2.1.S.4.2	Analytical Procedures
2.1.S.4.3	Validation of Analytical Procedures
2.1.S.4.4	Batch Analyses
2.1.S.4.5	Justification of specification
2.1.S.5	Reference Standards or Materials
2.1.S.6	Container Closure System
2.1.S.7	Stability

Investigation of medicinal products dossier (IMPD)

Pharmaceutical Technology

2.1.P	INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST
2.1.P.1	Description and Composition of the Medicinal Product
2.1.P.2	Pharmaceutical Development:
2.1.P.2.1	Components of the Medicinal Product
2.1.P.2.2	Medicinal Product
2.1.P.2.3	Manufacturing Process Development
2.1.P.2.4	Container Closure System
2.1.P.2.5	Microbiological Attributes
2.1.P.2.6	Compatibility
2.1.P.3	Manufacture:
2.1.P.3.1	Manufacturer(s)
2.1.P.3.2	Batch Formula
2.1.P.3.3	Description of Manufacturing Process and Process Controls
2.1.P.3.4	Controls of Critical Steps and Intermediates

Investigation of medicinal products dossier (IMPD)

Pharmaceutical Technology

2.1.P.3.5	Process Validation and/or Evaluation
2.1.P.4	Control of Excipients
2.1.P.4.1	Specifications:
2.1.P.4.2	Analytical Procedures
2.1.P.4.3	Validation of Analytical Procedures
2.1.P.4.4	Justification of Specifications
2.1.P.4.5	Excipients of Human or Animal Origin
2.1.P.4.6	Novel Excipients
2.1.P.5	Control of Medicinal Product:
2.1.P.5.1	Specification(s)
2.1.P.5.2	Analytical Procedures
2.1.P.5.3	Validation of Analytical Procedures
2.1.P.5.4	Batch Analyses
2.1.P.5.5	Characterization on impurities
2.1.P.5.6	Justification of Specification(s)
2.1.P.6	Reference Standards or Materials:
2.1.P.7	Container Closure System:
2.1.P.8	Stability:

Investigation of medicinal products dossier (IMPD)

Pharmaceutical Technology

2.1.A	APPENDICES
2.1.A.1	Facilities and Equipment
2.1.A.2	Adventitious Agents Safety Evaluation:
2.1.A.3	Novel Excipients:
2.1.A.4	Solvents for Reconstitution and Diluents:

INVESTIGATOR'S BROCHURE (IB; ICH GCP)

Pharmaceutical Technology

7.1 Introduction

7.2 General Considerations The IB should include:

7.2.1 Title Page

7.2.2 Confidentiality Statement

7.3 Contents of the Investigator's Brochure

7.3.1 Table of Contents

7.3.2 Summary

7.3.3 Introduction

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

INVESTIGATOR'S BROCHURE (IB; ICH GCP)

Pharmaceutical Technology

7.3.5 Nonclinical Studies
Introduction:
- Nature and frequency of pharmacological or toxic effects
- Severity or intensity of pharmacological or toxic effects
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- Dose response

Species tested
Number and sex of animals in each group
Unit dose (e.g., milligram/kilogram (mg/kg))
Dose interval
Route of administration
Duration of dosing
Information on systemic distribution
Duration of post-exposure follow-up
Results, including the following aspects:
(a) Nonclinical Pharmacology
(b) Pharmacokinetics and Product Metabolism in Animals
(c) Toxicology

INVESTIGATOR’S BROCHURE (IB; ICH GCP)

Pharmaceutical Technology

7.3.6 Effects in Humans
(a) Pharmacokinetics and Product Metabolism in Humans.
(b) Safety and Efficacy
(c) Marketing Experience
7.3.7 Summary of Data and Guidance for the Investigator
7.4 APPENDIX 1:
TITLE PAGE (Example)
SPONSOR'S NAME
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
INVESTIGATOR'S BROCHURE
Edition Number:
Release Date:
Replaces Previous Edition Number:
Date:

INVESTIGATOR'S BROCHURE (IB; ICH GCP)

Pharmaceutical Technology

7.5 APPENDIX 2:
TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

INVESTIGATOR'S BROCHURE (IB; ICH GCP)

Pharmaceutical Technology

7 Summary of Data and Guidance for the Investigator .....

NB: References on 1. Publications (These references should be found at the end of each chapter)

2. Reports

Appendices (if any)

Single dose

Repeated dose

Carcinogenicity

Special studies (e.g. irritancy and sensitisation)

Reproductive toxicity

Genotoxicity (mutagenicity)

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function).

Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).