e-ISSN: 2249-7625
Print ISSN: 2249-7633

International Journal of
Pharmacy Practice & Drug Research
www.ijppdr.com

FIRST REQUIREMENT FOR THE APPEAL OF ANTICANCER DRUG SUBMISSION PROCESS IN USA & EUROPE

Nagabhushanamma G*, Ramesh Reddy K, Umasankar K, Alagusundaram M, Jayachandra Reddy P

Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati-517605, Andhra Pradesh, India.

ABSTRACT

Medicinal products, pharmaceuticals, veterinary medicines, medical devices, and food supplements - all these products are subject to regulations designed by governments to protect public health. The Regulatory Affairs department ensures that their companies comply with all of the regulations and laws concerning their business. The Regulatory Affairs department is an important part of the organizational structure of pharmaceutical companies. Internally it liaises at the interphase of drug development, manufacturing, marketing and clinical research. Externally it is the key interface between the company and the regulatory authorities.

Keywords: Regulatory Affairs, Oncology, Common Technical Document, New drug.

INTRODUCTION

Regulatory Affairs is a specialized profession within the pharmaceutical/biotechnology sector. It oversees company compliance with regulations and laws pertaining to the manufacture, marketing and development of regulated products. Regulatory Affairs acts as point of contact between the company, its products and regulatory authorities and interacts with worldwide, federal, state, and local regulatory agencies (e.g., FDA (US), TGA (Australia), MHRA (UK), MCC (South Africa), etc) to assure…

1. Licensing
2. Registration
3. Development
4. Manufacturing
5. Marketing
6. Label of pharmaceutical and medical products are conducted in compliance with all applicable rules

Criteria for Regulations [1-3]

- It takes 8 to 15 years to develop a new drug/biologic product.
- Costs up to $ 800 million.
- Attention to early development, successfully execution of significant clinical studies helps to reduce number of development failures.
- A Regulatory affairs provides insight/guidance into this development through agency wisdom collected in guidance, previous experience, market precedence, etc.
- It helps to increase the safety & efficacy of drugs.
- Compliance with Regulator expectations therefore equates with development success. Patient Protection is of greatest importance.

Onclolgy

- Study of cancer is called oncology. Cancer is defined as abnormal and uncontrolled growth of body cells.
- The chemotherapeutic agent must be able to selectively kill or inhibit growth of neoplastic cells leaving normal cells unharmed.
- But currently available drugs damage DNA or interfere with DNA synthesis there by killing all rapidly dividing cells, both normal and cancerous. In addition, all approaches to cancer chemotherapy are ideally required to eradicate all tumour (cancer) cells completely.

Corresponding Author:- **Nagabhushanamma G** Email : gr419bhushana@gmail.com

Possible Side effects of Anticancer Drugs

- Anemia
- Tiredness
- Nausea, vomiting
- Mouth soreness
- Loss of appetite
- Hair loss
- Constipation or diarrhea
- Pain or nerve changes
- Changes in fertility & sexuality

Scope & Objective

Comparative study of Dossier compilation and submission process in USA & European Union Countries. To understand the regulatory guidelines in drug approval process. To understand the importance of regulatory guidelines. Comparative study of regulatory guidelines of USFDA & EMEA.

Dossier

There are many terms used internationally to describe a product dossier. These terms include: standard technical documentation, technical file, summary technical documentation, product summary file, product master file. Dossier is a file document submitted for the approval of Drug product. The product dossier is a selection of records and documents from this entire collection of records and documents that a manufacturer holds for a particular product. Manufacturers compile a product dossier from their existing technical documentation to provide evidence that the diagnostic conforms to the Essential Principles of Safety and Performance of Medical Devices. It is submitted in the CTD format. The content of the submitted product dossier should be traceable by the manufacturer for future reference.

CTD (Common Technical Document)

It is a harmonized format for presenting the data in ICH regions (International Conference on Harmonization). It is divided into 5 modules. They are as follows

Module 1 - Regional Administrative Information - Not a part of CTD

Module 2 - Clinical, Nonclinical overview & summary - Common to all countries

Module 3 - Quality - Common to all countries

Module 4 - Non clinical study reports - Common to all countries

Module 5 - Clinical study reports - Common to all countries

Module 1 - Regional Administrative Information

- It is country specific.
- It contains the information regarding the table of contents of submission, application forms
- Labeling specification etc.

Table 1. Module 1 as per EU Countries

Module	Section	Description
1	1.0	Cover Letter
	1.1	Comprehensive Table of Contents
	1.2	Application Form
	1.3	Product Information
	1.3.1	SPC, Labeling and Package Leaflet
	1.3.2	Mock-up
	1.3.3	Specimen
	1.3.4	Consultation with Target Patient Groups
	1.3.5	Product Information already approved in the Member States
	1.3.6	Braille
	1.4	Information about the Experts
	1.4.1	Quality
	1.4.2	Non-Clinical
	1.4.3	Clinical
	1.5	Specific Requirements for Different Types of Applications
	1.5.1	Information for Bibliographical Applications
	1.5.2	Information for Generic, 'Hybrid' or Bio-similar Applications
	1.5.3	(Extended) Data/Market Exclusivity
	1.5.4	Exceptional Circumstances
	1.5.5	Conditional Marketing Authorization
	1.6	Environmental Risk Assessment
	1.6.1	Non-GMO
	1.6.2	GMO
	1.7	Information relating to Orphan Market Exclusivity
	1.7.1	Similarity

	1.7.2	Market Exclusivity
	1.8	Information relating to Pharmacovigilance
	1.8.1	Pharmacovigilance System
	1.8.2	Risk-management System
	1.9	Information relating to Clinical Trials
	1.10	Information relating to Pediatrics

Table 2. Module 1 as per USFDA

Module	**section**	**Description**
1	Administrative part	
	1.1	Forms
	1.2	**Cover letters**
	1.3	**Administrative information**
	1.3.1	Contact/sponsor/applicant information
	1.3.1.1	**Change of address or corporate name**
	1.3.1.2	**Change in contact/agent**
	1.3.1.3	**Change in sponsor**
	1.3.1.4	**Transfer of obligation**
	1.3.1.5	**Change in ownership of an application or reissuance of license**
	1.3.2	Field copy certification
	1.3.3	Debarment certification
	1.3.4	Financial certification and disclosure
	1.3.5	Patent and exclusivity
	1.3.5.1	**Patent information**
	1.3.5.2	**Patent certification**
	1.3.5.3	**Exclusivity claim**
	1.3.6	Tropical disease priority review voucher
	1.4	**References**
	1.4.1	1 Letter of authorization
	1.4.2	Statement of right of reference
	1.4.3	List of authorized persons to incorporate by reference
	1.4.4	Cross-reference to previously submitted information
	1.5	**Application status**
	1.5.1	Withdrawal of an IND
	1.5.2	Inactivation request
	1.5.3	Reactivation request
	1.5.4	Reinstatement request
	1.5.5	Withdrawal of an unapproved BLA, NDA, ANDA, or Supplement
	1.5 6	Withdrawal of listed drug
	1.5.7	Withdrawal of approval of an application or revocation of license
	1.6	**Meetings**
	1.6.1	Meeting request
	1.6.2	Meeting background materials
	1.6.3	Correspondence regarding meetings
	1.7	Fast track
	1.7.	1 Fast track designation request
Module	section	Description
	1.7.2 l	Fast track designation withdrawal request
	1.7.3	Rolling review request
	1.7.4	Correspondence regarding fast track/rolling review
	1.8	Special protocol assessment request
	1.8.1	Clinical study
	1.8.2	Carcinogenicity study
	1.8.3	Stability study
	1.8.4	Animal efficacy study for approval under the animal rule
	1.9	Pediatric administrative information

	1.9.1	Request for waiver of pediatric studies
	1.9.2	Request for deferral of pediatric studies
	1.9.3	Request for pediatric exclusivity determination
	1.9.4	Proposed pediatric study request and amendments
	1.9.5	Proposal for written agreement (no longer applicable)
	1.9.6	Other correspondence regarding pediatric exclusivity or study plans
	1.10	Dispute resolution
	1.10.1	Request for dispute resolution
	1.10.2	Correspondence related to dispute resolution
	1.11	Information amendment: Information not covered under
	1.11.1	Quality information amendment
	1.11.2	Nonclinical information amendment
	1.11.3	Clinical information amendment
	1.11.4	Multiple module information amendment
	1.12	Other correspondence
	1.12.1	Pre IND correspondence
	1.12.2	Request to charge for clinical trial
	1.12.3	Request to charge for expanded access
	1.12.4	Request for comments and advice
	1.12.5	Request for a waiver
	1.12.6	Exception from informed consent for emergency research
	1.12.7	Public disclosure statement for exception from informed consent for
	1.12.8	Correspondence regarding exception from informed
	1.12.9	Notification of discontinuation of clinical trial
	1.12.10	Generic drug enforcement act statement
	1.12.11	ANDA basis for submission statement
	1.12.12	Comparison of generic drug and reference listed drug
	1.12.13	Request for waiver for in vivo studies
	1.12.14	Environmental analysis
	1.12.15	Request for waiver of in vivo bioavailability studies
	1.12.16	Field alert reports
	1.12.17	Orphan drug designation
	1.13	Annual report
	1.13.1	Summary for nonclinical studies
	1.13.2	Summary of clinical pharmacology information
	1.13.3	Summary of safety information
	1.13.4	Summary of labeling changes
	1.13.5	Summary of manufacturing changes
	1.13.6	Summary of microbiological changes
	1.13.7	Summary of other significant new information
	1.13.8	Individual study information
	1.13.9	General investigational plan
	1.13.10	Foreign marketing
	1.13.11	Distribution data
	1.13.12	Status of post marketing study commitments and requirements
	1.13.13	Status of other post marketing studies and requirements
	1.13.14	Log of outstanding regulatory business
	1.13.15	Development safety update report (DSUR)
	1.14	Labeling
	1.14.1	Draft labeling
	1.14.1.1	Draft carton and container labels
	1.14.1.2	Annotated draft labeling text
	1.14.1.3	Draft labeling text
	1.14.1.4	Label comprehension studies
	1.14.1.5	Labeling history
	1.14.2	Final labeling
	1.14.2.1	Final carton or container labels

	1.14.2.2	Final package insert (package inserts, patient information,
	1.14.2.3	Final labeling text
	1.14.3	Listed drug labeling
	1.14.3.1	Annotated comparison with listed drug
	1.14.3.2	Approved labeling text for listed drug
	1.14.3.3	Labeling text for reference listed drug
	1.14.4	Investigational drug labeling
	1.14.4.1	Investigational brochure
	1.14.4.2	Investigational drug labeling
	1.14.5	Foreign labeling
	1.14.6	Product labeling for 2253 submissions
Module	section	Description
	1.15	Promotional material <attribute = [promotional-material-
	1.15.1	Correspondence relating to promotional materials
	1.15.1.1	Request for advisory comments on launch materials
	1.15.1.2	Request for advisory comments on non-launch materials
	1.15.1.3	Pre submission of launch promotional materials for accelerated
	1.15.1.4	Pre submission of non-launch promotional materials for
	1.15.1.5	Promotional materials submitted pursuant to section 503B
	1.15.1.6	Response to untitled letter or warning letter
	1.15.1.7	Response to information request
	1.15.1.8	Correspondence accompanying materials previously missing or
	1.15.1.9	Withdrawal request
	1.15.1.10	Submission of annotated references
	1.15.1.11	General correspondence
	1.15.2	Materials <attribute = [promotional-material-doc-type]>
	1.15.2.1	Material <attribute = promotional-material-type>
	1.15.2.1.1	Clean version
	1.15.2.1.2	Annotated version
	1.15.2.1.3	Annotated labeling version
	1.15.2.1.4	Annotated references
	1.16	Risk management plan
	1.16.1	Risk Management (Non-REMS)
	1.16.2	Risk Evaluation and Mitigation Strategy (REMS)
	1.16.2.1	Final REMS
	1.16.2.2	Draft REMS
	1.16.2.3	REMS Assessment
	1.16.2.4	REMS Assessment Methodology
	1.16.2.5	REMS Correspondence
	1.16.2.6	REMS Modification History
	1.17	Post marketing studies
	1.17.1	Correspondence regarding post marketing commitments
	1.17.2	Correspondence regarding post marketing requirements
	1.18	Proprietary names
	1.19	Pre-EUA and EUA
	1.20	General investigational plan for initial IND

Table 3. Module 2: Summary of Quality as per Europe & US

Module	**Section**	**Description**
Module 2: Common Technical Document Summaries		
2	**2.2**	**Introduction to summary**
	2.3	**Quality overall summary**
	2.4	**Nonclinical overview**
	2.5	**Clinical overview**
	2.6	**Nonclinical written and tabulated summaries**
	2.6.1	Introduction

	2.6.2	Pharmacology written summary
	2.6.3	Pharmacology tabulated summary
	2.6.4	Pharmacokinetic written summary
	2.6.5	Pharmacokinetic tabulated summary
	2.6.6	Toxicology written summary
	2.6.7	Toxicology tabulated summary
	2.7	**Clinical summary**
	2.7.1	Summary of Biopharmaceutical Studies and Associated Analytical
	2.7.2	Summary of Clinical Pharmacology studies
	2.7.3	Summary of Clinical Efficacy [indication]
	2.7.4	Summary of Clinical Safety
	2.7.5	References
	2.7.6	Synopses of individual studies

Table 4. Module 3: Quality as per Europe & US

Module	Section	Description
3	**3.2**	**Body of data**
	3.2.S	Drug substance [name, manufacturer]
	3.2.S.1	**General information**
	3.2.S.1.1	Nomenclature
	3.2.S.1.2	Structure
	3.2.S.1.3	General properties
	3.2.S.2	**Manufacture**
	3.2.S.2.1	Manufacturer(s)
	3.2.S.2.2	Description of Manufacturing Process and Process Controls
	3.2.S.2.3	Control of Materials
	3.2.S.2.4	Controls of Critical Steps and Intermediates
	3.2.S.2.5	Process Validation and/or Evaluation
	3.2.S.2.6	Manufacturing Process Development
	3.2.S.3	Characterization
Module	Section	Description
	3.2.S.3.1	Elucidation of Structure and other Characteristics
	3.2.S.3.2	Impurities
	3.2.S.4	Control of drug substance
	3.2.S.4.1	Specification
	3.2.S.4.2	Analytical Procedures
	3.2.S.4.3	Validation of Analytical Procedures
	3.2.S.4.4	Batch Analyses
	3.2.S.4.5	Justification of Specification
	3.2.S.5	Reference standards or materials
	3.2.S.6	Container closure systems
	3.2.S.7	Stability
	3.2.S.7.1	Stability Summary and Conclusions
	3.2.S.7.2	Post Approval Stability Protocol and Stability Commitment
	3.2.S.7.3	Stability Data
	3.2.P	Drug product [name, dosage form, manufacturer]
	3.2.P.1	Description and composition of the drug product
	3.2.P.2	Pharmaceutical development
	3.2.P.3	Manufacture
	3.2.P.3.1	Manufacturer(s)
	3.2.P.3.2	Batch Formula
	3.2.P.3.3	Description of Manufacturing Process and Process Controls
	3.2.P.3.4	Controls of Critical Steps and Intermediates
	3.2.P.3.5	Process Validation and/or Evaluation
	3.2.P.4	Control of excipients [name]
	3.2.P.4.1	Specification(s)

	3.2.P.4.2	Analytical Procedures
	3.2.P.4.3	Validation of Analytical Procedure
	3.2.P.4.4	Justification of Specifications
	3.2.P.4.5	Excipients of Human or Animal Origin
	3.2.P.4.6	Novel Excipients
	3.2.P.5	Control of drug product
	3.2.P.5.1	Specification(s)
	3.2.P.5.2	Analytical Procedures
	3.2.P.5.3	Validation of Analytical Procedures
	3.2.P.5.4	Batch Analyses
	3.2.P.5.5	Characterization of Impurities
	3.2.P.5.6	Justification of Specification(s)
	3.2.P.6	Reference standards or materials
	3.2.P.7	Container closure system
	3.2.P.8	Stability
	3.2.P.8.1	Stability Summary and Conclusion
	3.2.P.8.2	Post approval Stability Protocol and Stability Commitment
	3.2.P.8.3	Stability Data
	3.2.A	Appendices
	3.2.A.1	Facilities and Equipment [name, manufacturer]
	3.2.A.2	Adventitious agents safety evaluation [name, dosage form, manufacturer]
	3.2.A.3	Novel excipients
	3.2.R	Regional information
	3.3	Literature references

Table 5. Module 4: Nonclinical Study Reports as per Europe & US

Module	Section	Description
	4.2	**STUDY REPORTS**
	4.2.1	Pharmacology
	4.2.1.1	Primary Pharmacodynamics
	4.2.1.2	Secondary Pharmacodynamics
	4.2.1.3	Safety Pharmacology
	4.2.1.4	Pharmacodynamic Drug Interactions
	4.2.2	Pharmacokinetics
	4.2.2.1	Analytical Methods and Validation Reports (if separate reports are available)
	4.2.2.2	Absorption
	4.2.2.3	Distribution
	4.2.2.4	Metabolism
	4.2.2.5	Excretion
	4.2.2.6	Pharmacokinetic Drug Interactions (nonclinical)
	4.2.2.7	Other Pharmacokinetic Studies
	4.2.3	Toxicology
	4.2.3.1	Single-Dose Toxicity (in order by species, by route)
	4.2.3.2	Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
	4.2.3.3	Genotoxicity
	4.2.3.3.1	In vitro
	4.2.3.3.2	In vivo (including supportive toxicokinetics evaluations)
	4.2.3.4	Carcinogenicity (including supportive toxicokinetics evaluations)
	4.2.3.4.1	Long-term studies (in order by species; including range finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
	4.2.3.4.2	Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat dose toxicity or pharmacokinetics)
	4.2.3.4.3	Other studies
	4.2.3.5	Reproductive and Developmental Toxicity (including range-

		finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly)
	4.2.3.5.1	Fertility and early embryonic development
	4.2.3.5.2	Embryo-fetal development
	4.2.3.5.3	Prenatal and postnatal development, including maternal function
	4.2.3.5.4	Studies in which the offspring (juvenile animals) are dosed and /or further evaluated.
	4.2.3.6	Local Tolerance
	4.2.3.7	Other Toxicity Studies (if available)
	4.2.3.7.1	Antigenicity
	4.2.3.7.2	Immunotoxicity
	4.2.3.7.3	Mechanistic studies (if not included elsewhere)
	4.2.3.7.4	Dependence
	4.2.3.7.5	Metabolites
	4.2.3.7.6	Impurities
	4.2.3.7.7	Other
	4.3	LITERATURE REFERENCES

Table 6. Module 5: Clinical Study Reports as per Europe & US

Module	Section	Description
5	5.1	Table of Contents of Module 5
	5.2	Tabular Listing of All Clinical Studies
	5.3	Clinical Study Reports
	5.3.1	Reports of Biopharmaceutic Studies
	5.3.1.1	Bioavailability (BA) Study Reports
	5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports
	5.3.1.3	In vitro-In vivo Correlation Study Reports
	5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
	5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
	5.3.2.1	Plasma Protein Binding Study Reports
	5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies
	5.3.2.3	Reports of Studies Using Other Human Biomaterials
	5.3.3	Reports of Human Pharmacokinetic (PK) Studies
	5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports
	5.3.3.2	Patient PK and Initial Tolerability Study Reports
	5.3.3.3	Intrinsic Factor PK Study Reports
	5.3.3.4	Extrinsic Factor PK Study Reports
	5.3.3.5	Population PK Study Reports
	5.3.4	Reports of Human Pharmacodynamic (PD) Studies
	5.3.4.1	Healthy Subject PD and PK/PD Study Reports
	5.3.4.2	Patient PD and PK/PD Study Reports
	5.3.5	Reports of Efficacy and Safety Studies
	5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
	5.3.5.2	Study Reports of Uncontrolled Clinical Studies
	5.3.5.3	Reports of Analyses of Data from More Than One Study
	5.3.5.4	Other Clinical Study Reports
	5.3.6	Reports of Post-Marketing Experience
	5.3.7	Case Report Forms and Individual Patient Listings
	5.4	Literature References

Table 7. Differences between European and USFDA drug agencies

S. No	EMEA	USFDA
1.	Multiple agencies a)European Medicines Evaluation Agency b)Committee For Medicinal Products For Human Use. c) National Health Agencies.	One agency.

2.	Multiple registration process a) National b)Centralized procedure c)Decentralized procedure d)Mutual recognition procedure	One registration process
3.	TSE/BSE data is required.	TSE/BSE data is not required.
4.	Braille code is required on labeling.	Braille code is not required on labeling.
5.	Median time for marketing submission to approval is 350 days	Median time for marketing submission to approval is 182 days
6.	The average time taken by EMA to approve a drug product was 366 days	The average time taken by FDA to approve a drug product was 322 days

Table 8. Comparative study of dossier submission in Europe &US

S. No	**Requirements**	**USA**	**Europe**
A. Administrative			
1	Application	NDA/ANDA	MAA
2	Debarment certification	Required	Not required
3	No. of copies	3	1
4	Approval time line	11Month	12 Month
5	Fees	125 US $ per product	10-20 lakhs
6	presentation	eCTD & paper	eCTD
B. Finished Product Control			
1	Justification	ICHQ6A	ICHQ6A
2	Assay	90%-100%	95%-105%
3	Disintegration	Not required	Required
4	Color Identification	Not required	Required
5	Water content	Required	Not required
S.NO	**Requirements**	**USA**	**Europe**
C. Manufacturing & Controls			
1	No. of batches	01	03
2	Packaging	A minimum of 1,00,000units	Not required
	Process validation	Not required at the time of	Required
	Batch size	A minimum of 1,00,000 units	A minimum of 1,00,000 units
D. Stability			
1	No. of batches	01	02
2	Condition	25/60:40/75	25/60:40/75
3	Date &Time of submission	3 Month accelerated & 3Month long term	6 Month accelerated & 6Month long term
4	Container Orientation	Inverted upright	Not address
5	Clause	21CFR part 210& 211	Volume 4 European guidelines for medicinal products
6	Qp certification	Not required	Required
E. Bioequivalence			
1	CRO	Audited by FDA	Audited by MHRA
	Reserved sample	5 times the sample required	No such sample is
	Fasted/Fed	Must be as per OCG	No such requirement
4	Retention of samples	5 year from the date of filing the application	No such requirement but usually followed

Fig. 1. CTD

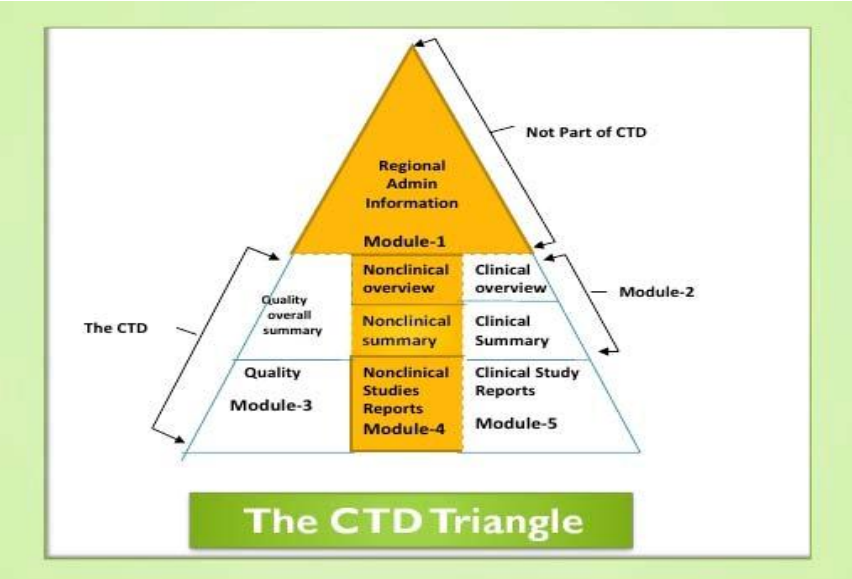


Fig. 2 Drug approval process in USA

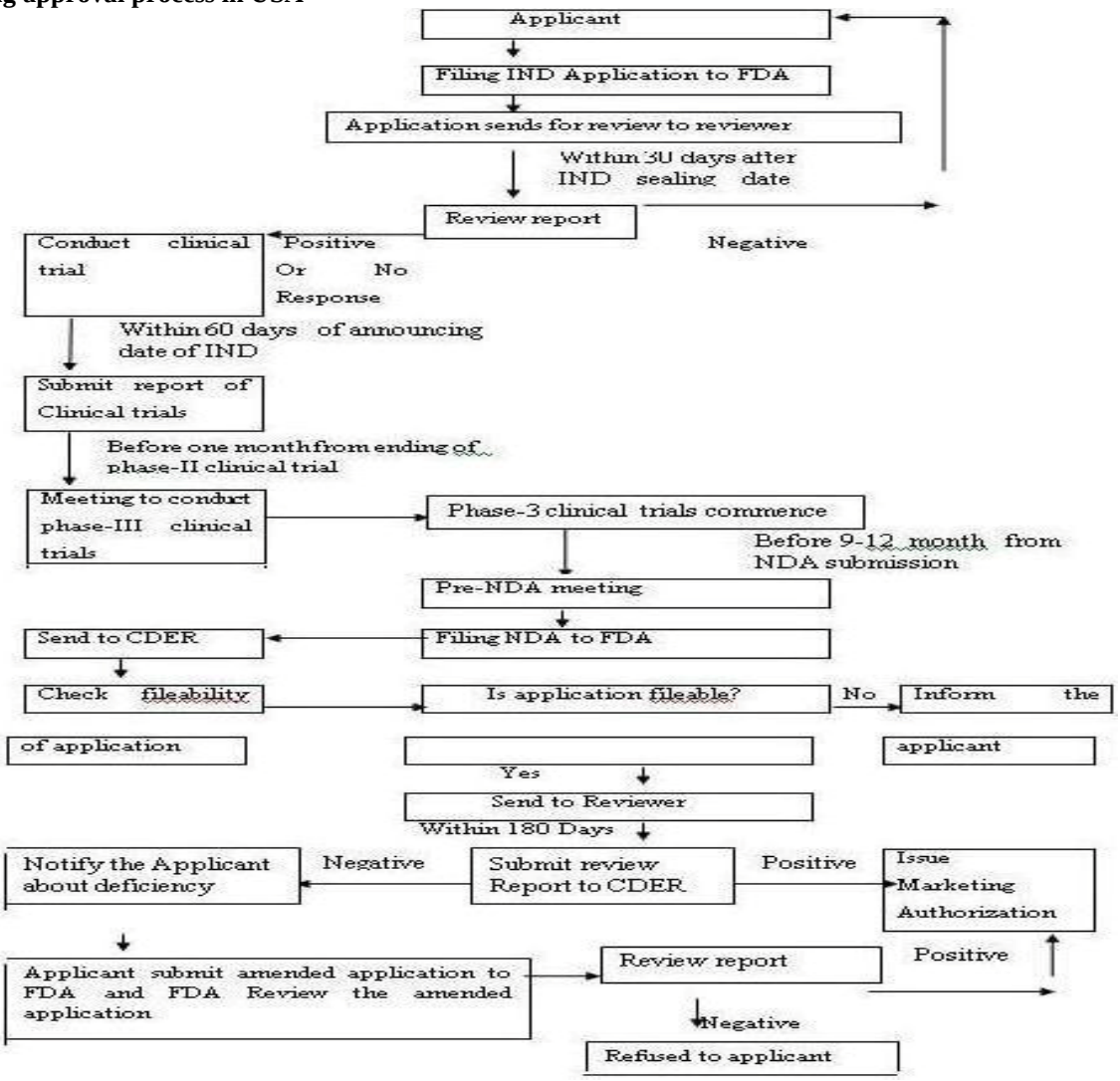


Fig. 3. Drug Development Path

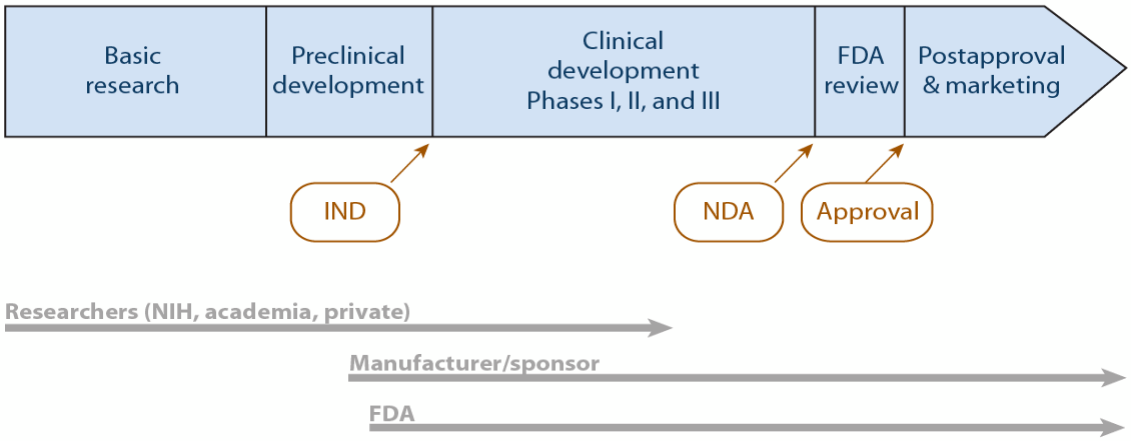
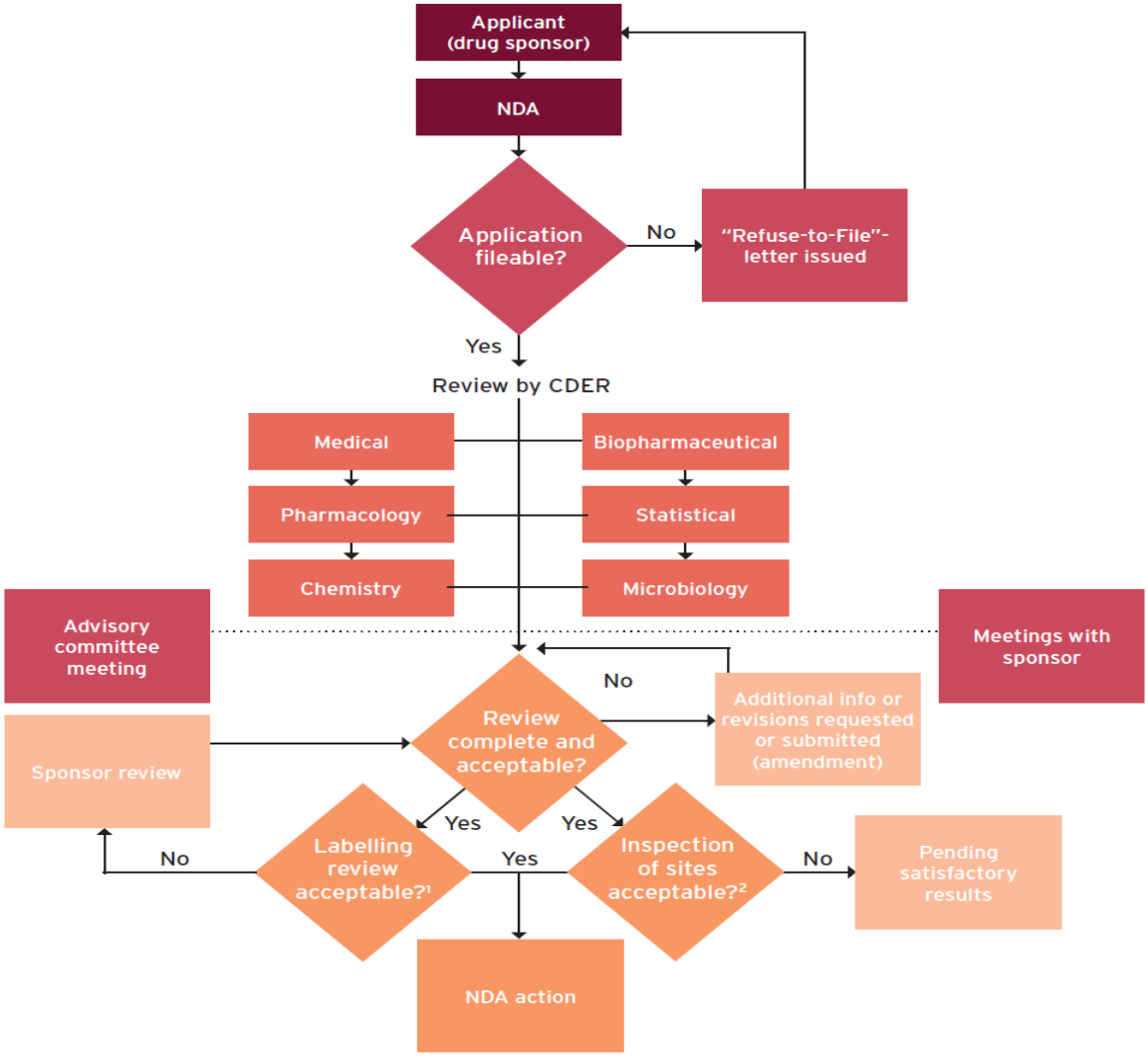


Fig. 4. New Drug Application Review Process



(1) Labelling in this context means offical instructions for use
(2) Manufacturing sites and sites where significant clinical trials are performed

Fig. 5. Drug Approval Procedure by Decentralized Procedure in Europe

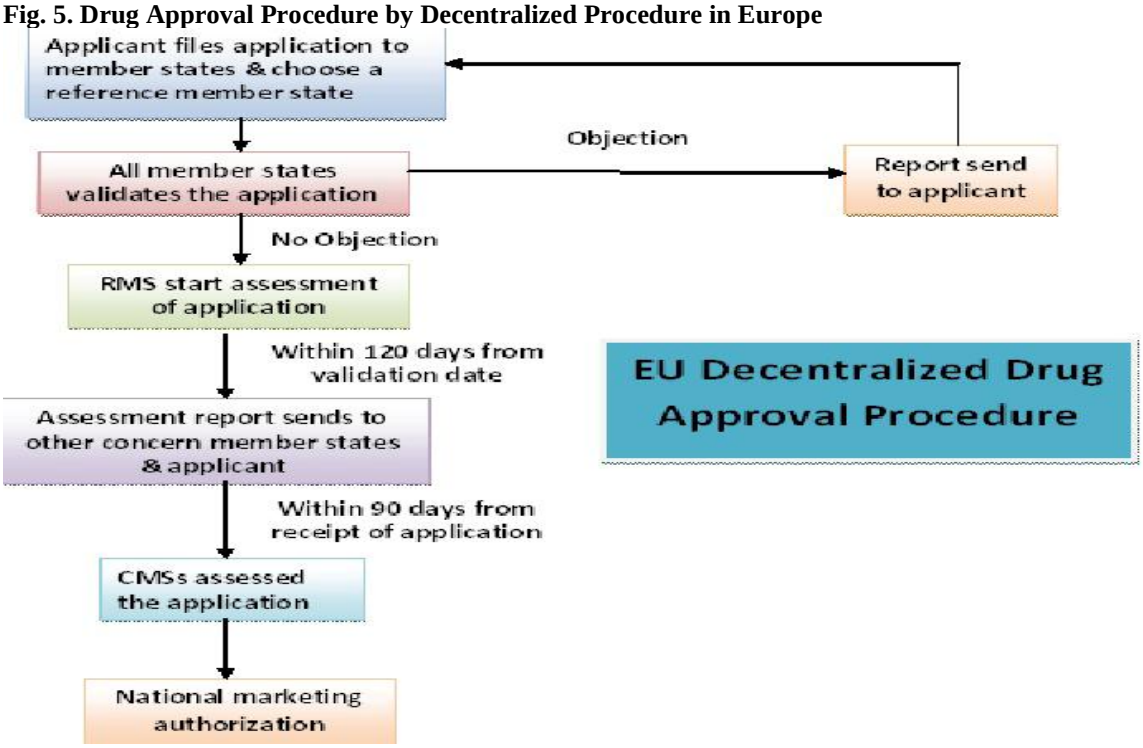


Fig. 6. Drug Approval Procedure by centralized Procedure in Europe

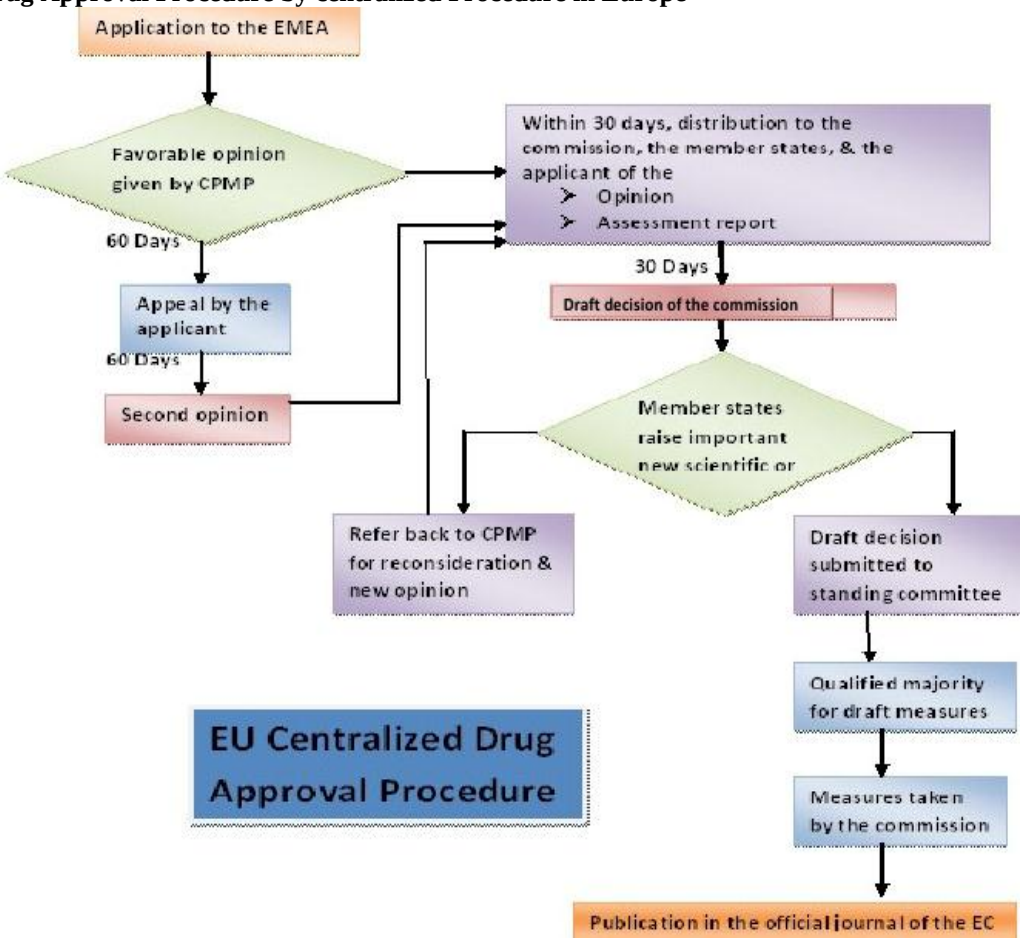


Fig. 7. Validation Procedure

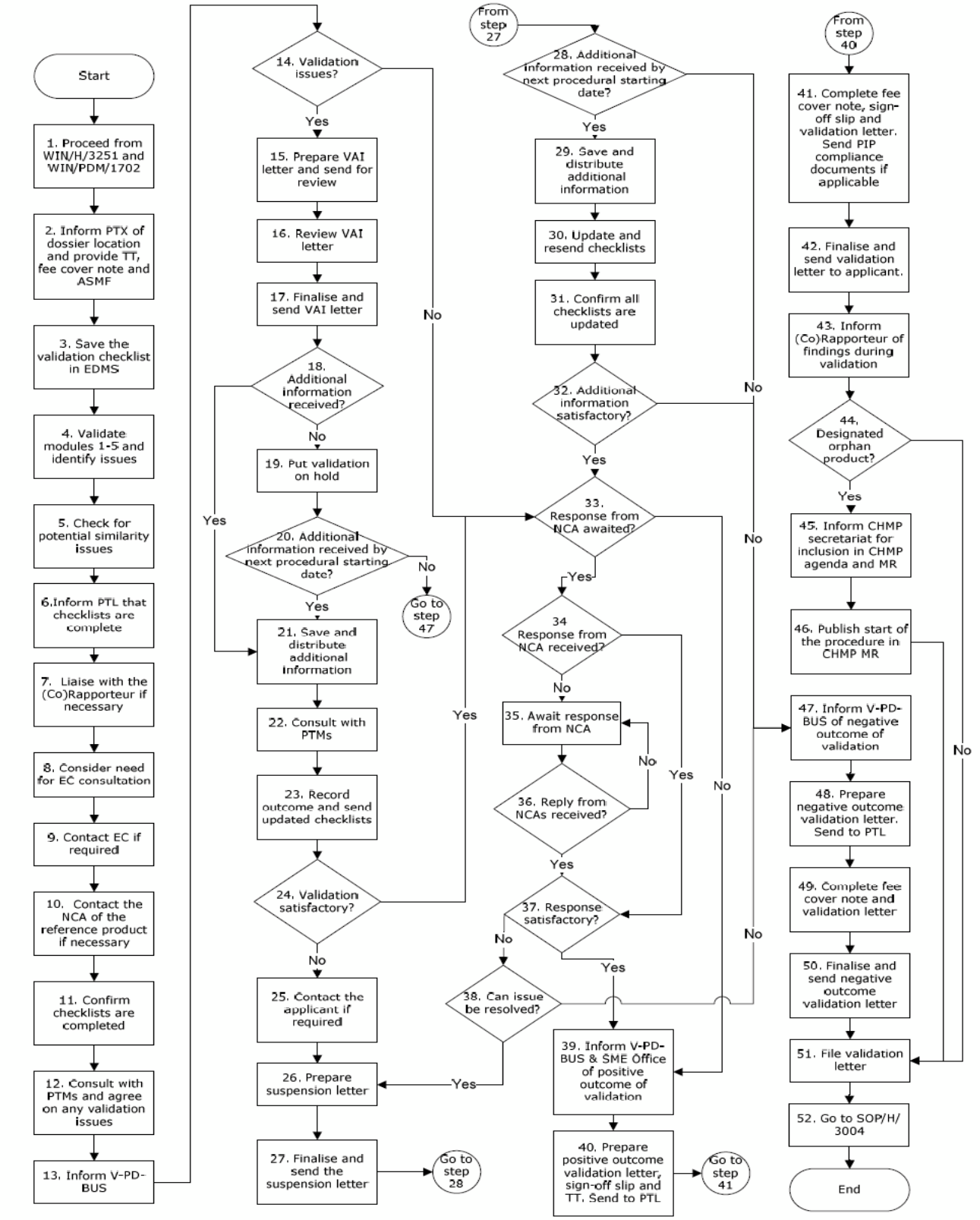
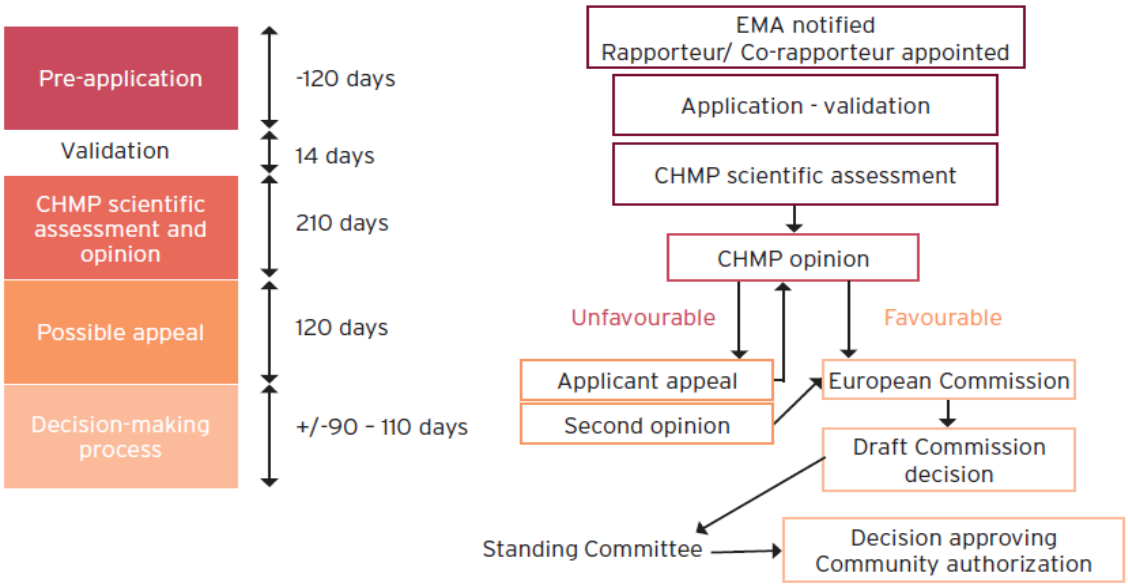


Fig. 8. Centralized procedure



Method of Drug Approval process [4-9]

Anticancer drug submission process in USA

- USFDA (United States Food and Drug Administration) is a regulatory agency within the Department of Health and Human Services in United States. A key responsibility is to regulate the safety and effectiveness of drugs sold in the United States. FDA divides that responsibility into two phases: Preapproval (premarket).
- Post approval (post market).
- FDA reviews manufacturers' applications to market drugs in the United States a drug may not be sold unless it has FDA application.

The Standard Process of Drug Approval

FDA follows four steps to approve a new drug for marketing into untied states.

Preapproval (pre market)

- Investigational New Drug (IND) Application
- Clinical development
- New Drug Application.(NDA)
- FDA review

Investigational New Drug (IND) Application:

Before testing in humans called clinical testing—the drug's sponsor (usually its manufacturer) must file an investigational new drug (IND) application with FDA. The IND includes information about the proposed clinical study design, completed animal test data and the lead investigator's qualifications. The application must include an "Indication for Use" section that describes what the drug does and the clinical condition and population for which the manufacturer intends its use. Trial subjects should be representative of that population. The FDA has 30 days to review an IND application. Unless FDA objects, a manufacturer may then begin clinical testing.

Clinical development

Phase I clinical trials: In FDA's words, "to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects". If the sponsor considers the product still worthy of investment, it continues with Phase II and Phase III clinical trials. Those trials gather evidence of the drug's efficacy and effectiveness in larger groups of individuals with the particular characteristic, condition, or disease of interest while continuing to monitor safety.

New Drug Application (NDA)

Once a manufacturer completes the clinical trials, it submits a new drug application (NDA) to FDA's Center for Drug Evaluation and Research (CDER). The NDA contains not only the clinical trial results, but also information about the manufacturing process and facilities, including Quality control and assurance procedures.

Use of the NDA

1. The drug is safe and effective in its proposed use, and whether the benefits outweigh the risks.
2. The drug's proposed labeling (package insert) is appropriate, and what it should contain.
3. The methods used in manufacturing the drug and the

controls used to maintain the drug's Quality is adequate to preserve the drug's identity, strength, quality and purity.

Main part of NDA submission

There can be up to 15 different sections in an NDA

1. Index
2. Summary
3. Chemistry, Manufacturing and Controls
4. Samples, Methods validation Package and Labeling
5. Non-Clinical Pharmacology and Toxicology
6. Human Pharmacokinetics and Bioavailability
7. Microbiology (for anti-microbial drugs only
8 Clinical Data—including controlled clinical trials, uncontrolled clinical studies and other Studies
9. Safety Update Report
10. Statistics
11. Case Report Tabulations
12. Case Report Forms
13. Patent Information
14. Patent Certification
15. Other Information

FDA Review Process

The goals of the review are to determine if the results of well- controlled studies provide substantial evidence of effectiveness, and if the results show the product is safe under the conditions of use in the proposed labeling.

The NDA review process consists of five phases:

1. Filing determination and review planning
2. Review
3. Advisory committee preparation and conduct (where applicable)
4. Action phase
5. Post-action phase

1. Filing determination and review planning (days 0 to 74):

The primary goals of the filing determination and review planning process are to determine whether the submitted application meets the regulatory requirements for filing. The outcome of this stage is either acceptance of filing, or a refusal to file if issues that are identified cannot be resolved with the sponsor. Typically by day 45, the decision on accepting a file will have been made. By day 45, the FDA attempts to have conducted an internal planning meeting for the review.

2. Review

The FDA review process consists of two reviews.

- Primary Review
- Secondary Review

Primary Review

The primary review can often involve a reanalysis of data or additional analyses presented by the sponsor. Ex: certain patients that a sponsor may have included as "evaluable" may not be considered evaluable by the FDA reviewer, so additional statistical analyses may be performed on different sets or subsets of patients.

Secondary Review

A secondary review is also conducted in which the secondary reviewer summarizes the primary review and writes his own recommendations. The written opinion by the secondary reviewer is optional for biologic drugs unless the secondary reviewer disagrees with the opinions of the primary reviewer. FDA has 180 days to review an NDA. If it finds deficiencies, such as missing information, the clock stops until the manufacturer submits the additional information. If the manufacturer cannot respond to FDA's request (e.g., if a required study has not been done, making it impossible to evaluate safety or effectiveness of the drug), the manufacturer may voluntarily withdraw the application. If and when the manufacturer is able to provide the information, the clock resumes and FDA continues the review.

Special Mechanisms to Expedite the Development and Review Process

Not all reviews and applications follow the standard procedures. For drugs that address unmet needs or serious diseases or conditions, FDA regularly uses three formal mechanisms to expedite the development and review process.

Accelerated approval

FDA regulations allow "accelerated approval" of a drug or biologic product that provides a "meaningful therapeutic benefit over existing treatments." The rule covers two situations. The first allows approval to be based on clinical trials that, rather than using standard outcome measures such as survival or disease progression, use "a surrogate endpoint that is reasonably likely ... to predict clinical benefit". The second situation addresses drugs whose use FDA considers safe and effective only under set restrictions that could include limited prescribing or dispensing. FDA usually requires post marketing studies of products approved this way.

Fast track

The Food and Drug Administration Modernization Act of 1997 (FDAMA, P.L. 105-115) directed the Secretary to create a mechanism whereby FDA could designate as "Fast Track" certain products that meet two criteria. First, the product must concern a serious or life-threatening condition; Second, it must have the potential to address an unmet medical need.

Once FDA grants a Fast Track designation, it encourages the manufacturer to meet with the agency to discuss development plans and strategies before the

formal submission of an NDA. Such early interaction can help clarify elements of clinical study design and presentation that if absent at NDA submission could delay approval decisions. However, FDA makes similar interactions available to any sponsor who seeks FDA consultation throughout the stages of drug development.

Priority review

Unlike Fast Track or Accelerated Approval, the Priority Review process begins only when a manufacturer officially submits an NDA. Priority Review, therefore, does not alter the timing or content of steps taken in a drug's development or testing for safety and effectiveness. Although Priority Review is not explicitly required by law, FDA has established it in practice, and various statutes, such as the Prescription Drug User Fee Act (PDUFA), refer to and sometimes require it. When FDA determines that a product would address an unmet need, it places it through Priority Review. That designation results in an average turnaround time (from completed application to approval decision) of approximately 6 months, rather than the 10-month average for Standard Review

3. Advisory committee preparation and conduct (where applicable)

Advisory committee meetings are typically required in the following situations:

1. The review concerns new molecular entities, especially if a product is the first member of a new drug class.
2. The clinical study design uses novel clinical or surrogate endpoints.
3. The application raises significant issues about the safety or effectiveness of the drug.
4. The application raises significant public health questions on the role of the drug or biologic in the diagnosis, cure, mitigation, treatment or prevention of disease.

4. Action Phase

- The FDA summarizes all review activity and a preliminary decision is made on the regulatory action. Consideration is given to risk management, major labeling issues and post-marketing commitments.
- During this phase, the determinations from the review help form the basis for discussion on the labeling of products that are expected to be approved. The labeling discussions are typically expected to occur about three weeks prior to division sign-off.
- During this time, if necessary, negotiation of post-marketing commitments and negotiation of the risk management program take place. The action letter (i.e., Approval or Complete Response) is then drafted and internally reviewed prior to sign-off.
- The final action is sent to the sponsor, ideally by the PDUFA (Prescription Drug User Fee Act) date. The PDUFA date is the FDA's target time to complete its review and provide a decision on the application to the sponsor.

5. Post-action phase

The goal is to learn from the review process and identify what was successful and what can be improved upon. This phase may involve meetings with the sponsor to clarify deficiencies and what is expected in a response, if the final decision was not an approval letter.

Anticancer Drug Approval process in Europe

Types of Marketing Authorization In EU Countries

Different types of marketing authorization are available when seeking approval to market a new drug in European market. They are as follows

1. National authorization procedure.
2. Decentralized procedure.
3. Mutual recognition procedure.
4. Centralized procedure.

National authorization procedure

This type of authorisation is granted on country by country basis by competent authorities, in each member state. Products only intended for one market will follow this procedure.

Decentralized procedure

By this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country.

Mutual recognition procedure

A product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

Centralized procedure

A marketing authorization granted under the centralized procedure is valid for the entire Community market, which means the medicinal product may be put on the market in all Member States.

Advantages

Allows a pharmaceutical company to market its pharmaceutical products in all member states. Without having to obtain Approval from each member state.

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.
- Orphan medicinal products.
- Medicinal products containing new active substances for the following indications: AIDS, cancer neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases.
- For medicines that do not fall within these categories, companies have the option of submitting an application for a centralised marketing authorisation to the Agency, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorisation would be in the interest of public or animal health.

Justification

Anticancer drugs are submitted in Europe by the centralized procedure.(Medicinal product containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases). The European Parliament and of the Council lays down a centralized Community procedure for the authorization of medicinal products, for which there is A single application; A single evaluation; A single authorization; Access to the single market of the Community.

Generic Drug Submission

- A generic or hybrid medicinal product of a reference medicinal product authorized via the centralised procedure has 'automatic' access to the centralized procedure.
- Multiple/duplicate or informed consent applications from the same or different marketing authorization holder for a specific medicinal product with an active substance(s) already authorized via the centralised procedure, have automatic access to the centralized procedure.

Application Form

The application form is to be used for an application for a marketing authorization of a medicinal product for human use submitted to (a) the European Medicines Agency under the centralized procedure or (b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition procedure or decentralized procedure.

Procedure for application of anticancer drugs in Europe [10-12]

Presubmission

At least seven months before submission, applicants should notify the EMEA of their intention to submit an application and give a realistic estimate of the month of submission. In that notification applicants should include:

- A draft summary of product characteristics;
- A justification of the product's eligibility for evaluation under the centralized procedure (if not already requested at an earlier stage)
- In case of 'generic' or 'bio-similar' applications, details of the proposed Reference medicinal product used throughout the quality, safety and efficacy development programme (as appropriate).

Validation [13,14]

SOPs and WIN

1. SOP/H/3004 on Tasks of product team on handling of initial Marketing Authorization Application.
2. SOP/H/3101 on Determination of Fees (Medicinal products for Human Use).
3. SOP/H/3106 on Core master files of medicinal products for human and veterinary use following the centralized procedure.
4. SOP/H/3181 on Assessment of similarity of medicinal products.
5. SOP/H/3271 Handling of the compliance check with an agreed pediatric investigation plan
6. WIN/ADM/7009 on Hard copy files pharmaceutical industry.
7. WIN/H/3251 on Handling of Electronic-only submissions, including eCTDs, using the European Review System (EURS).
8. WIN/PDM/1702 on Processing of incoming submissions related to medicinal products for Human use.

Timetable for the evaluation

Once the application is validated and provided the Rapporteur and Co-Rapporteur have confirmed that they have received the dossier (including any additional information requested during validation phase), the EMEA starts the procedure at the monthly starting date published on the EMEA website. If the Rapporteur and the Co-Rapporteur have not received their copies of the dossier and/or additional Validation information on the day where the dossier is validated by the EMEA, the start of the procedure may be delayed until the procedural starting date of the next month. If, within a month from the start of the procedure, any other member of the CHMP has not received the requested parts of the dossier from the applicant, the EMEA will stop the clock until confirmation is received that each member of the CHMP has been delivered the requested documentation. It is therefore important that applicants are able to provide a proof of delivery to Rapporteur, Co- Rapporteur and to CHMP members (upon request) to the EMEA. Having taken into consideration the standard timetable agreed by the CHMP

for the evaluation of a centralized application, a timetable is prepared by the EMEA in consultation with the Rapporteur and the Co-Rapporteur. This timetable is then proposed to the CHMP for adoption. The EMEA shall ensure that the opinion of the CHMP is given within 210 days (less any clock- stops for the applicant to provide answers to questions from the CHMP). The role of the SAGs is to provide, on request from the CHMP, an independent recommendation on scientific and technical matters relating to products under evaluation or any other scientific issues relevant to the work of the CHMP. While views expressed by the SAGs are taken into account, the ultimate responsibility for final opinions rests with the CHMP.

The Committee's Opinion

On or before Day 210, the CHMP adopts its opinion in the light of the final recommendation of the Rapporteur and Co-Rapporteur and further evidence presented at the oral explanation. In case of an oral explanation and where the procedural timetable allows, the CHMP Opinion will be adopted at the following CHMP meeting, allowing applicant, (Co-) Rapporteur and CHMP members to finalise the product information and Assessment Report as appropriate. The applicant should liaise with the PTL on the practical arrangements in connection with the adoption of the opinion. The draft opinion is prepared by the EMEA and then adopted by the CHMP. The CHMP opinion, which may be favorable or unfavorable, is, wherever possible, reached by scientific consensus. The Rapporteur and the Co-Rapporteur, in co-ordination with the PTL, taking account of the full scientific debate within the CHMP and the conclusions reached, prepares the final assessment report, which, once adopted by the CHMP, becomes the CHMP assessment report and is appended to the CHMP opinion.

RESULTS AND DISCUSSION

Analyses of new antineoplastic agents approved in the US and EU

- We identified 95 new antineoplastic agents were approved in the US between 1999-2013(June)
- In EU 85 new antineoplastic agents were approved between 1999 and 2013
- Antineoplastic agents were approved in the US, with an average of 3.92 antineoplastic agents approved per year and in the EU a total of 44 new antineoplastic agents were approved, with an average of 3.38 antineoplastic agents approved per year.

CONCLUSION

What's encouraging is that while total development time for oncology and non-oncology drugs decreased by half a year during the 2002-11 period, for oncology drugs this was accomplished by process improvements that shortened regulatory review time. Oncology drug development continues to be challenging, due to smaller patient populations for recruitment and longer periods for evaluation of treatment response. The percentage of approval of new antineoplastic agents was more than 90% for the US and almost 80% for the EU. The US was the first to approve the majority of the new antineoplastic agents, and the EU was slightly delayed.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics 2002. *CA Cancer J Clin*, 55, 2005,74-108.
2. CDER, CBER, US FDA. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007: 1-22.
3. Anonymous 1. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications.
4. FDA, "Inside Clinical Trials: Testing Medical Products in People; What Is a Clinical Trial?" Information for Consumers, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm.
5. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (*Official Journal L 136, 30/4/2004 p. 1 -33*): http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf
6. Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community code relating to medicinal products for human use as amended by Directive2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC.:http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/consol_2004/human_code.pdf
7. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use(Official Journal L 159, 27/6/2003 p. 46 - 94): http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf
8. 8.The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1 on "Marketing authorisation".

9. The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4, Chapter 6 on “Centralised Procedure”.
10. Procedural Advice on the CHMP/CAT Rapporteur/Co-Rapporteur Appointment Principles, Objective Criteria and Methodology in Accordance with Article 62(1) of Regulation (EC) No. 726/2004 (EMA/151751/2010).
11. "Guideline on the categorisation of New Applications versus Variation Applications”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C.
12. Regulation (EC) No 726/2004.
13. The linguistic review process of product information in the centralised procedure – human (EMEA/5542/02).
14. EMEA/553631/2007: Procedural advice for validation of new marketing authorisation application - extension/variation application and compliance check with an agreed PIP. (http://www.ema.europa.eu/pdfs/human/paediatrics/55363107en.pdf).