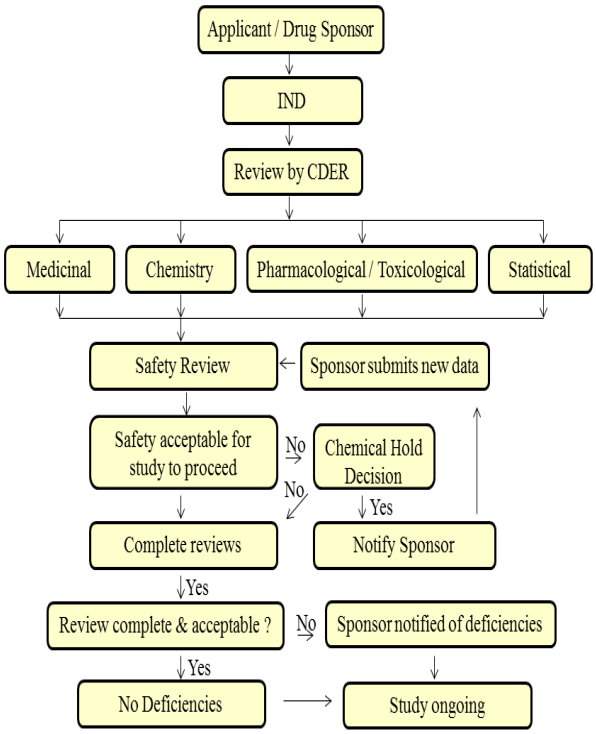
REGULATORY APPROVAL PROCESS

Introduction:

For small molecule drugs, the path to a marketed drug involves a long and exhaustive journey through basic research, discovery of the medicine, pre-clinical development tests, increasingly completed clinical trials with humans and regulatory approval by the regulatory authority

Investigational new drug (IND):

It's an application filled to the FDA in order to start clinical trials in a human if the drug was found to be safe from the reports of pre-clinical trials. The federal food, drug and cosmetics act regulated through title 21 of U. S. code of federal regulations, requires a new drug to be approved by FDA before legally getting introduce into the market.



Investigational New Drug Application (IND)

Types of INDs:

A. Commercial INDs

B. Non-commercial (research) INDs

1. Investigators IND

2. Emergency use IND

3. Treatment IND

The IND application must contain information in three board areas:

1.animal pharmacology and toxicologist studies: pre-clinical data to access if the product is reasonable is safe for initial testing in humans.

2. Manufacturing information: information pertaining to composition, manufacturer, stability and controls used for manufacturing drug product to ensure that the company can adequately produce and supply consistent batches.

3. Clinical protocol and investigator information: detailed protocols for proposed clinical studies to make sure subjects are not exposed to undue risk. Also, information on the qualifications of the investigators (chiefly physicians) if the full field their clinical duties

An IND most also include the investigators brochure.

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Format and content of IND:

1. Cover sheet form (FDA 1571)

2.Table of contents

3. Introductory statement and general investigational plan.

4. Investigators brochure.

5. Protocols.

6. Chemistry, manufacturing and control information.

7. Pharmacology and toxicology information.

8. Previous human experience with IP.

9. Additional information.

New drug application (NDA):

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 sale the drug in the United State.

The new drug application is the vehicle through which the drug sponsors finally propose FDA to approve a new investigational drug for sale and marketing after phase 3 a pivot trials.

The following letter codes describe the review priority of the drug:

- S- standard review: for drugs similar to currently available drugs.
- P- priority review: for drugs that represent significant advances over existing treatment

Classification of drugs in NDA:

Centre of drug evolution and research (CDER) classifies new drug application.

- New molecular entity.
- New salt of previously approved drug.
- New formulation of previously approved drug.
- New combination of two or more drugs.
- Already marketed drugs product duplication.
- New indication for already marketed drug.
- Already marketed drug product.

General requirements for feeling of NDA:

A. An archival copy: it is a complete copy of application submission that serves as its permanent record.

B. Review copy: it is divided into 6 technical sections-

1. Chemistry, manufacturing and controls (CMC).
2. Non clinical pharmacology and toxicology.
3. Human pharmacokinetics and bioavailability.

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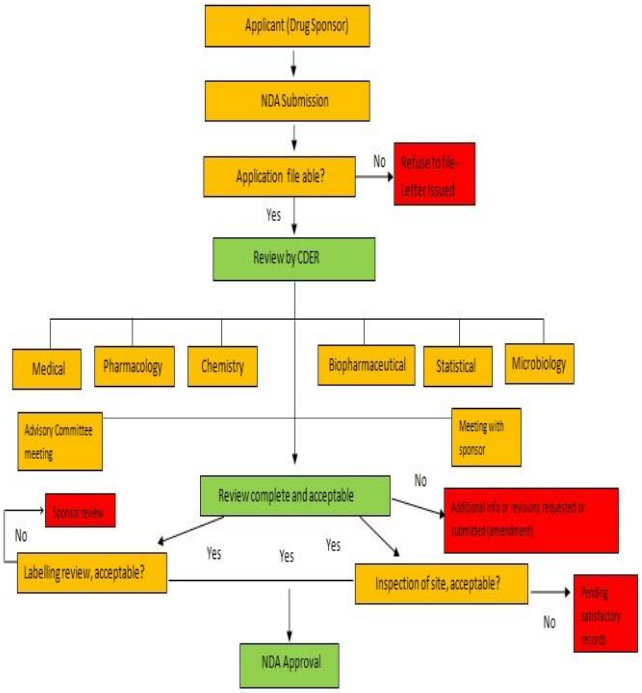
4. Microbiology.
5. Clinical data.
6. Statistical.



ABBREVIATED NEW DRUG APPLICATION (ANDA):

It's an application made for approval of generic drug. The sponsor is not required to reproduce the clinical studies that were done for original brand name product.

Instead, generic drug manufacturers must demonstrate that their product is the same as and bio equivalent to a previously approved brand name product.

Code of federal regulations:

21 CFR 314: APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR ANTIBIOTIC DRUG.

21 CFR 320: bioavailability and bio equivalence requirements.

21CFR 310: new drugs

Office of generic drugs (OGD) strongly encourages submission of equivalence, chemistry and labelling portion of application in electronic format.

Under section 314.94 (a) (12), the pattern certification includes one of the following:

I. Paragraph I certification.
II. Paragraph II certification.
III. Paragraph III certification.
IV. Paragraph IV certification

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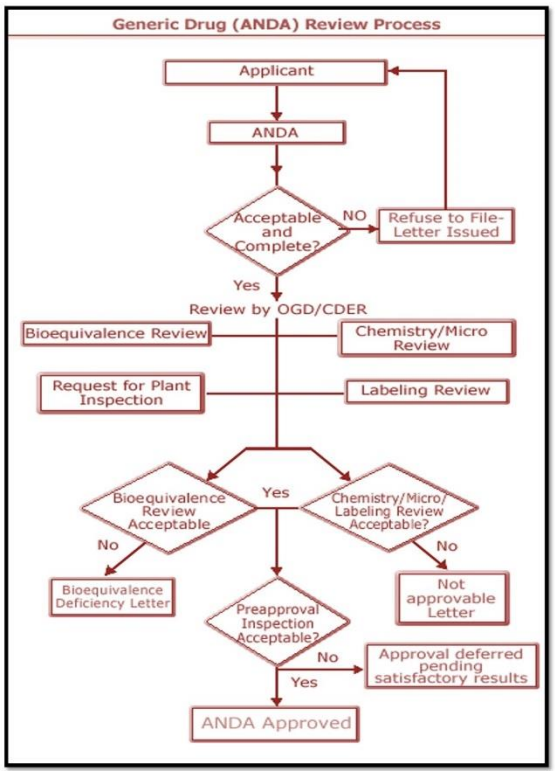

❖ Drug approval in Europe:

1. Centralise procedure:

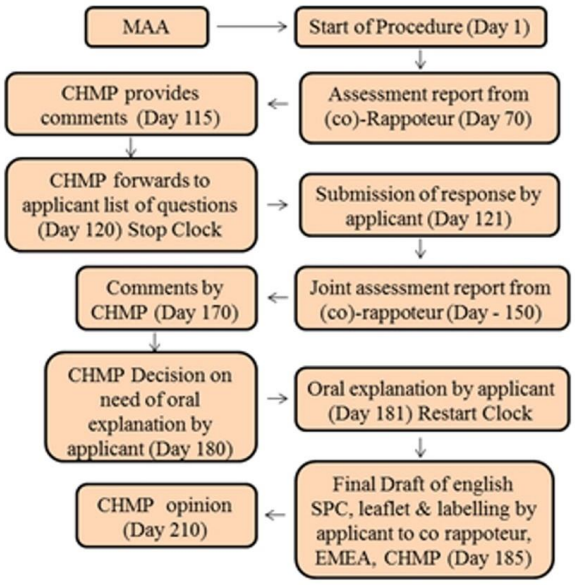

Figure 5: Flow chart of Centralized Procedure

2. Mutual recognition procedure

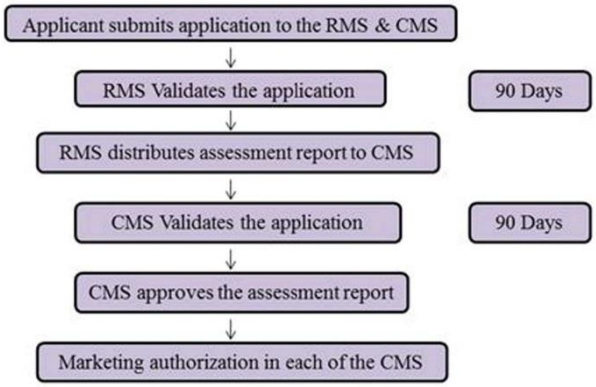

Figure 6: Flow chart of Mutual Recognition Procedure

3. Decentralized procedure

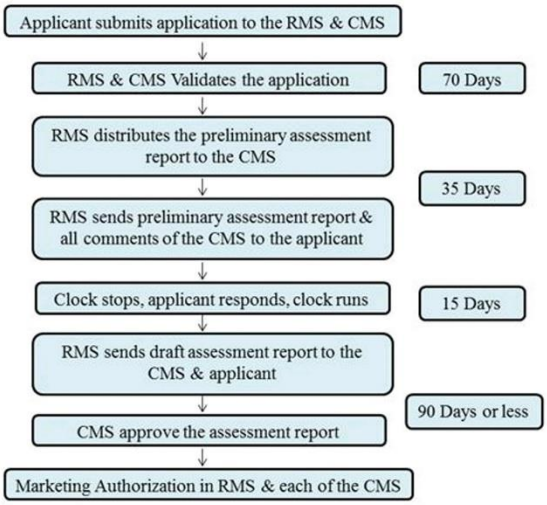

Figure 7: Flow chart of Decentralized Procedure

4. Nationalised procedure:

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

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

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CHANGES TO AN APPROVED NDA/ANDA

In November 1999 FDA issued a guidance document entitled "changes to an approved NDA or ANDA." In April 2004 the agency issues its first revision of document which takes the place of the original document. These recommendations include post approval changes in:

- Components and composition
- Manufacturing sites
- Manufacturing processes
- Specifications
- Container closure system
- Labelling

Overview of regulatory Authorities India, USA and EU

Table 1: Principle differences between US, EU & INDIA

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	TSE/BSE Study data not required	TSE/BSE Study data required	TSE/BSE Study data required
Braille code	Braille code is not required on labelling	Braille code is required on labelling	Braille code is not required on labelling
Post-approval changes	Post-approval changes in the approved drug: • Minor changes • Moderate changes • Major changes	Post-variation in the approved drug: • Type IA Variation • Type IB Variation • Type II Variation	Post approval changes: Major quality changes Moderate quality changes

Table 2: Administrative Requirements

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	12 - 18 Months
Fees	Under $2 million-NDA Application $51,520 – ANDA Application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS: £99,507	50,000 INR
Presentation	eCTD & Paper	eCTD	Paper

Table 3: Finished Product Control Requirements

Requirements	US	EU	INDIA
Justification	ICH Q6A	ICH Q6A	ICH Q6A
Assay	90 - 100 %	95 - 105 %	90 - 110 %
Disintegration	Not Required	Required	Required
Colour Identification	Not Required	Required	Required
Water Content	Required	Not Required	Required

Table 4: Manufacturing & Control Requirements

Requirements	US	EU	INDIA
Number of batches	1	3	1
Packaging	A minimum of 1,00,000 Units	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

Table 5: Stability Requirements

Requirements	US	EU	INDIA
Number of batches	3 Pilot Batch or 2 Pilot Batch & 1 Small scale	2 Pilot Scale (If API Stable) 3 Primary Batches (If API unstable)	2 Pilot Scale/Production scale(If API Stable) 3 Primary Batches (If API unstable)
Condition: Long term stability, Accelerated stability,	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months); Intermediate: 30°C/65%RH	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months) Intermediate: 30°C/65%RH	Long term: 30°C/70%RH Accelerated:40°C/75%RH (0,3,6 months)
Minimum time period at Submission	6 Months Accelerate & 6 Months long term	6 Months Accelerate & 6 Months long term	6 Months Accelerate & 6 Months long term
Container orientation	Inverted & Upright	Do not address	upright and inverted
Clause	21 CFR part 210 & 211	Volume 4 EU Guidelines for medicinal products	ICH Q1F
QP Certification	Not Required	Required	Required

Table 6: Bioequivalence Requirements

Requirements	US	EU	INDIA
CRO (Audits)	Audited by FDA	Audited by MHRA	CDSCO
Reserve Sample	5 times the sample required for analysis	No such requirement	-
Fasted / Fed	Must be as per OGD recommendation	No such requirement	As CDSCO recommendation
Retention of samples	5 years from date of filing the application	No such requirement	3 years from date of filing the application
BE study for generic drugs	Against US RLD in any country. To refer 'BE recommendations' in FDA site for guidance.	Against EU reference product (ERP) in any country	Against US/EU/Australia RLD in any country except Thailand, where BE to be done locally against local reference product.

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