FORMATTING, ASSEMBLING & SUBMISSION OF NEW DRUG APPLICATION

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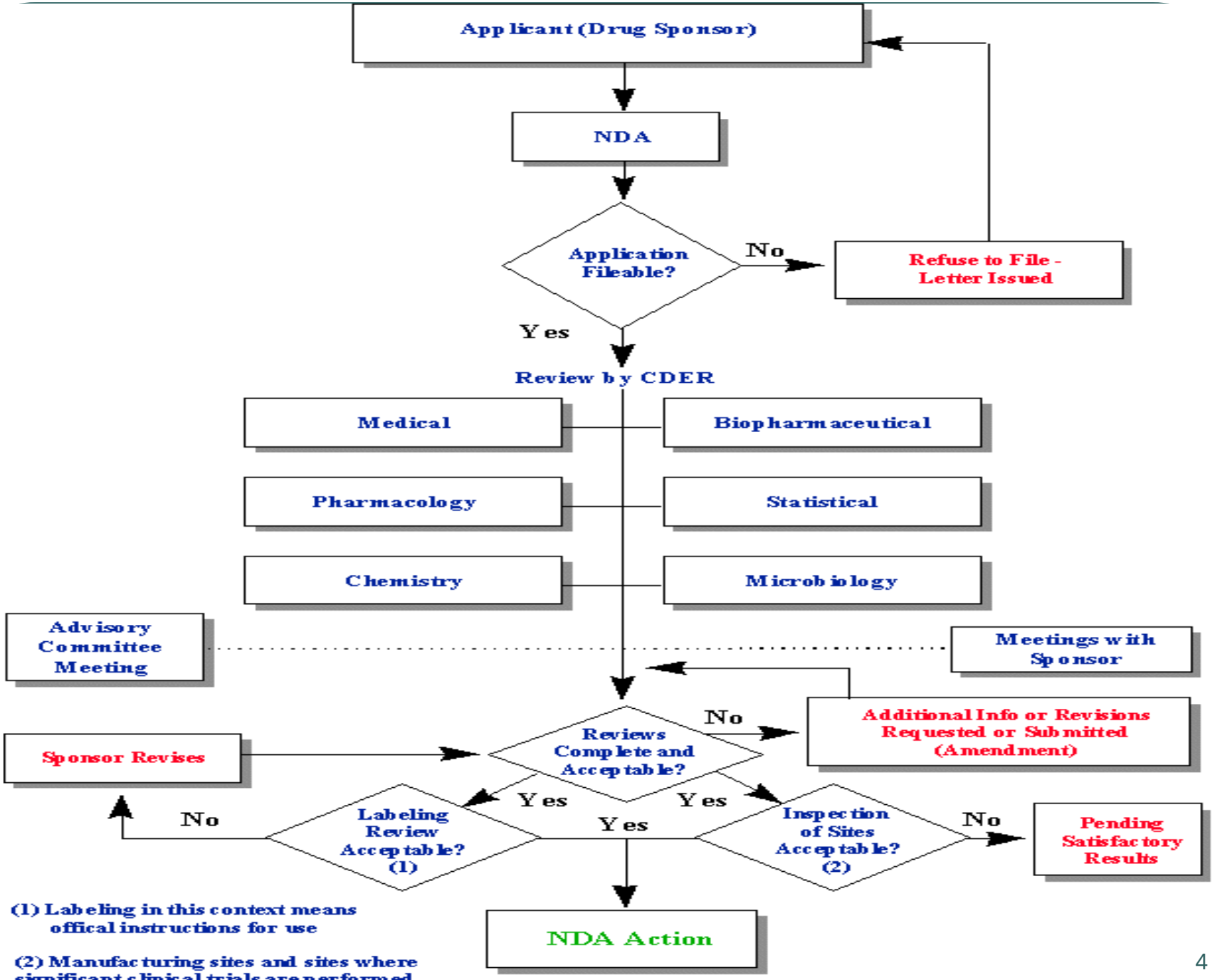
- The US Food & drug administration requires drug sponsors to submit an NDA for review before a new pharmaceutical can be approved for marketing and sale in USA

- The NDA contains clinical and non clinical test data, analytical reports, drug chemistry information and description of manufacturing procedures.

NDA Classifications

- New Molecular Entity
- New Salt of Previously Approved Drug (not a new molecular entity)
- New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
- New Combination of Two or More Drugs
- Already Marketed Drug Product - Duplication (i.e., new manufacturer)
- New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription to OTC)
- Already Marketed Drug Product - No Previously Approved NDA


Applicant (Drug Sponsor)
NDA
Application Fileable?
No
Refuse to File - Letter Issued
Yes
Review by CDER
Medical
Biopharmaceutical
Pharmacology
Statistical
Chemistry
Microbiology
Advisory Committee Meeting
Meetings with Sponsor
Reviews Complete and Acceptable?
No
Additional Info or Revisions Requested or Submitted (Amendment)
Sponsor Revises
Yes
Yes
Yes
Labeling Review Acceptable? (1)
No
Inspection of Sites Acceptable? (2)
No
Pending Satisfactory Results
NDA Action
(1) Labeling in this context means offical instructions for use
(2) Manufacturing sites and sites where significant clinical trials are performed

FORMAT FOR US NDA

Cover letter

1. Index
2. Labeling
3. Application summary

RIEVEW SECTIONS

4. Chemistry
5. Non Clinical Pharmacology & Toxicology
6. Human P.K Bioavailability
7. Clinical Microbiology
8. Clinical data
9. Safety update report
10. Statistical data
11. Case report tabulations
12. Case report forms
13. Patient information
14. Patient certification
15. Establishment description
16. Debarment Certification
17. Field copy certificate
18. User fee cover sheet
19. Financial disclosure
20. Other/ Pediatric

Index:

- It is a comprehensive table of contents that enables reviewers to find specific information in this massive document.

Labeling:

- This section must include all the draft labeling that is intended for use on product container, packings including the proposed package insert.
- NDA must have four copies of graft labeling.

Section 3 - Application summary

- It is abbreviated version of the entire application. The summary consists of 50-200 pages.
- It must include **proposed annotated package insert** and must contain the following sections

1. Description
2. Clinical pharmacology
3. Indications and usage
4. Contraindications
5. Drug abuse and dependence
6. Dosage and administration
7. Clinical data summary
8. Warnings
9. Warnings
10. Precautions
11. Adverse reactions
12. Over dosage
13. Microbiology summary

Section 4: Chemistry, Manufacturing & Controls

This section includes description of drug substance

- Generic name
- Chemical name
- Molecular structure & formula
- Molecular weight
- Appearance, M.P. & B.P.
- Refractive index, viscosity & specific gravity.
- Polymorphs
- Solubility
- Synthesis scheme & description.

Section 5: Non clinical pharmacology & toxicology

- This section should provide individual study reports, including pharmacology, toxicology and ADME studies.

Section 6: Human Pharmacokinetics and Bioavailability

- This section includes data from Phase –I studies.
- The summary should address all bioavailability and pharmacokinetic data.
- This section also includes data on drug information, analytical methods used in *in vivo* biopharmaceutics study.

Section 7 : Microbiology.

- This section is required only for anti infective drug products.
- This section requires following technical information
- Complete description of biochemical basis of drug action on microbial physiology.
- The drugs anti microbial spectrum
- Clinical microbiology laboratory methods.

Section-8: Clinical data

- This section consists of

- Background / overview of clinical investigation.
- Clinical pharmacology
- Controlled clinical trials
- Un controlled clinical trials
- Other studies and information
- Integrated summary of effectiveness data.
- Integrated summary of safety information.
- Drug abuse and over dosage information.
- Integrated summary of benefits and risks of the drug.

Section- 10 : Statistics

- This section includes documentation of the statistical analyses performed to evaluate the controlled clinical trials and other safety information.

Section-11: case report form tabulations

- This include complete tabulations for each patient from phase- II & phase-III efficacy study and from phase-I clinical pharmacology study

Section 12:Case report forms

- It is necessary to include CRF for each patient who died during the study and who were dropped from the study due to adverse events.

ANDA

"A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use"

It termed "abbreviated" because they generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

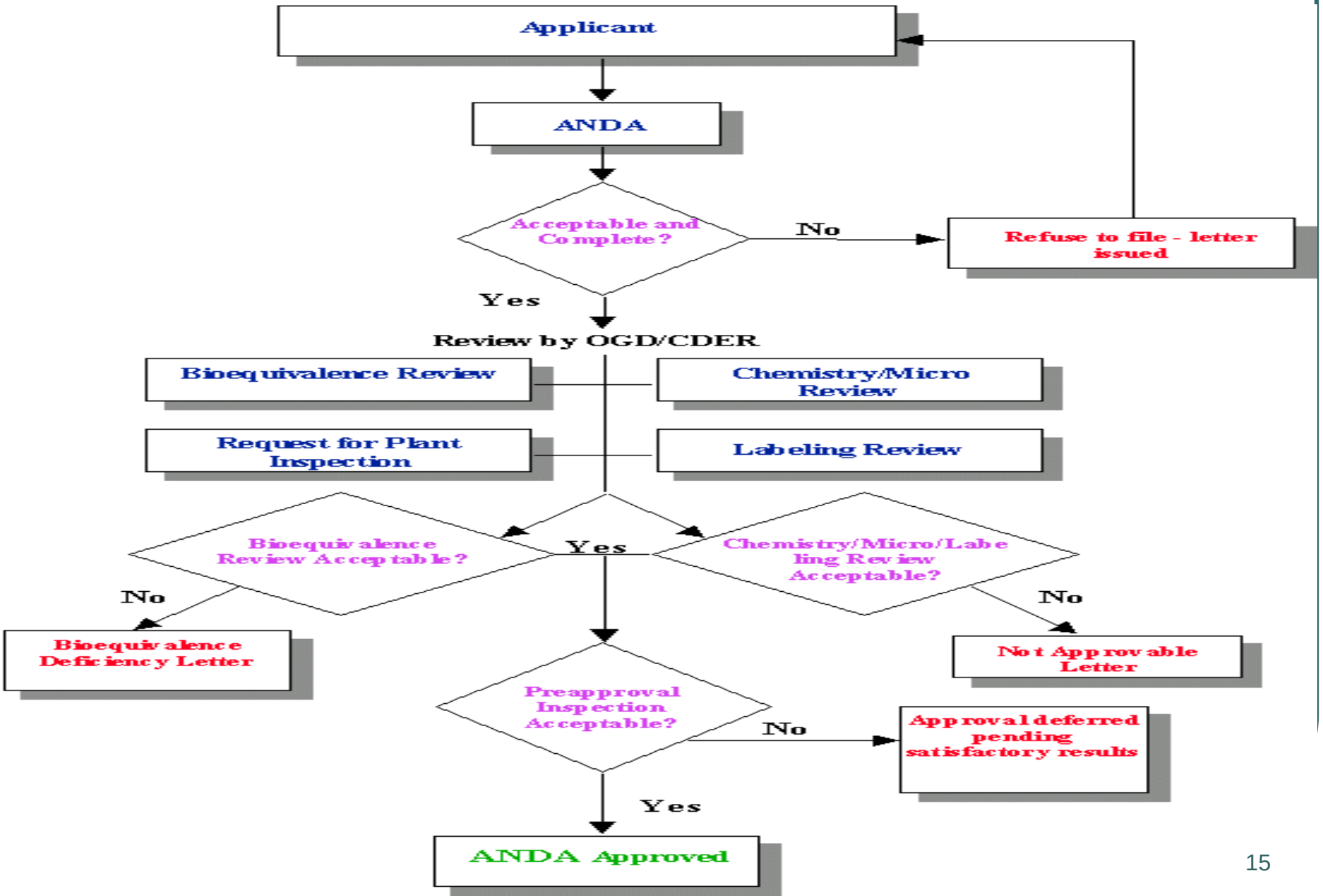
Basic Generic Drug Requirements are:--

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Inactive ingredients already approved in a similar NDA

Goal of ANDA

- To reduce the price of the drug.
- To reduce the time development.
- Increase the bioavailability of the drug in comparison to references list drug.

ANDA Review process



NDA vs. ANDA Review Process

NDA Requirement	ANDA Requirement
1. Labeling	1. *Labeling*
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies	
10. Clinical Studies	9. Bioequivalence
11. Bioavailability	