DOCUMENTATION IN PHARMACEUTICAL INDUSTRY

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DOCUMENTATION IN PHARMACEUTICAL INDUSTRY

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Introduction

- Documentation is a systematic procedure of preparation, checking, verifying, issuing, storing and reviewing of any documents
- The basic rules in any good manufacturing practice (GMP) regulations specify that the pharmaceutical manufacturer must maintain proper documentation and records.
- Documentation helps to build up a detailed picture of what a activity has done in the past and what it is doing now and, thus, it provides a basis for planning what it is going to do in the future
- Effective documentation enhances the visibility of the quality assurance system.

Purpose of Documentations

- Defines specifications and procedures for all materials and methods of manufacture and control
- Ensures all personnel know what to do and when to do it
- Ensure that authorized persons have all information necessary for release of product
- Ensures documented evidence, traceability, provide records and audit trail for investigation
- Ensures availability of data for validation, review and statistical analysis.

General Requirements

- Good documentation constitutes an essential part of the quality assurance system.
- Clearly written procedures prevent errors resulting from spoken communication, and clear documentation permits tracing of activities performed.
- Documents must be designed, prepared, reviewed, and distributed with care.
- Documents must be approved, signed, and dated by the appropriate competent and authorized persons.
- Documents must have unambiguous contents. The title, nature, and purpose should be clearly stated. They must be laid out in an orderly fashion and be easy to check. Reproduced documents must be clear and legible.
- Documents must be regularly reviewed and kept up-to-date. When a document has been revised, systems must be operated to prevent inadvertent use of superseded documents (e.g., only current documentation should be available for use).
- Documents must not be handwritten; however, where documents require the entry of data, these entries may be made in clear legible handwriting using a suitable indelible medium (i.e., not a pencil). Sufficient space must be provided for such entries
- Any correction made to a document or record must be signed or initialed and dated; the correction must permit the reading of the original information. Where appropriate, the reason for the correction must be recorded

- Record must be kept at the time each action is taken and in such a way that all activities concerning the conduct of preclinical studies, clinical trials, and the manufacture and control of products are traceable.
- Storage of critical records must at secure place, with access limited to authorized persons. The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, etc.
- Records which are critical to regulatory compliance or to support essential business activities must be duplicated on paper, microfilm, or electronically, and stored in a separate, secure location in a separate building from the originals.
- Date may be recorded by electromagnetic or photographic means, but detailed procedures relating to whatever system is adopted must be available.
- Accuracy of the record should be checked as per the defined procedure. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, access must be restricted by passwords or other means, and entry of critical data must be independently checked.
- It is particularly important that during the period of retention, the data can be rendered legible within an appropriate period of time.
- If data is modified, it must be traceable

Good Manufacturing Practices

- GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use
- Worldwide, there are different official regulatory statements and guidelines for GMP for pharmaceutical products.
- They may be regulations (as in the US, Japan, or Korea), directives (as in the EU), guides (as in the UK), codes (as in Australia), or a WHO code (as in many Southeast Asia Countries).
- Among them, the following stand out as the most influential and most frequently referenced:
  - The US Current Good Manufacturing Practices for Finished Pharmaceuticals regulations (the US cGMPs)
  - The Guide to Good Manufacturing Practice for Medicinal Products of the European Union (the EC GMP Guide)
  - The ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
  - The World Health Organization (WHO) good manufacturing practices

- The other guidelines and regulations referred by the pharmaceutical manufacturers are as under:
  - Schedule M 'Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products,'
  - The Drugs and Cosmetics Act and Rules, India
  - PIC/S Guide to Good Manufacturing Practice for Medicinal Products.
  - Center for Drug Evaluation and Research (CDER): Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients

The 10 golden rules of GMP

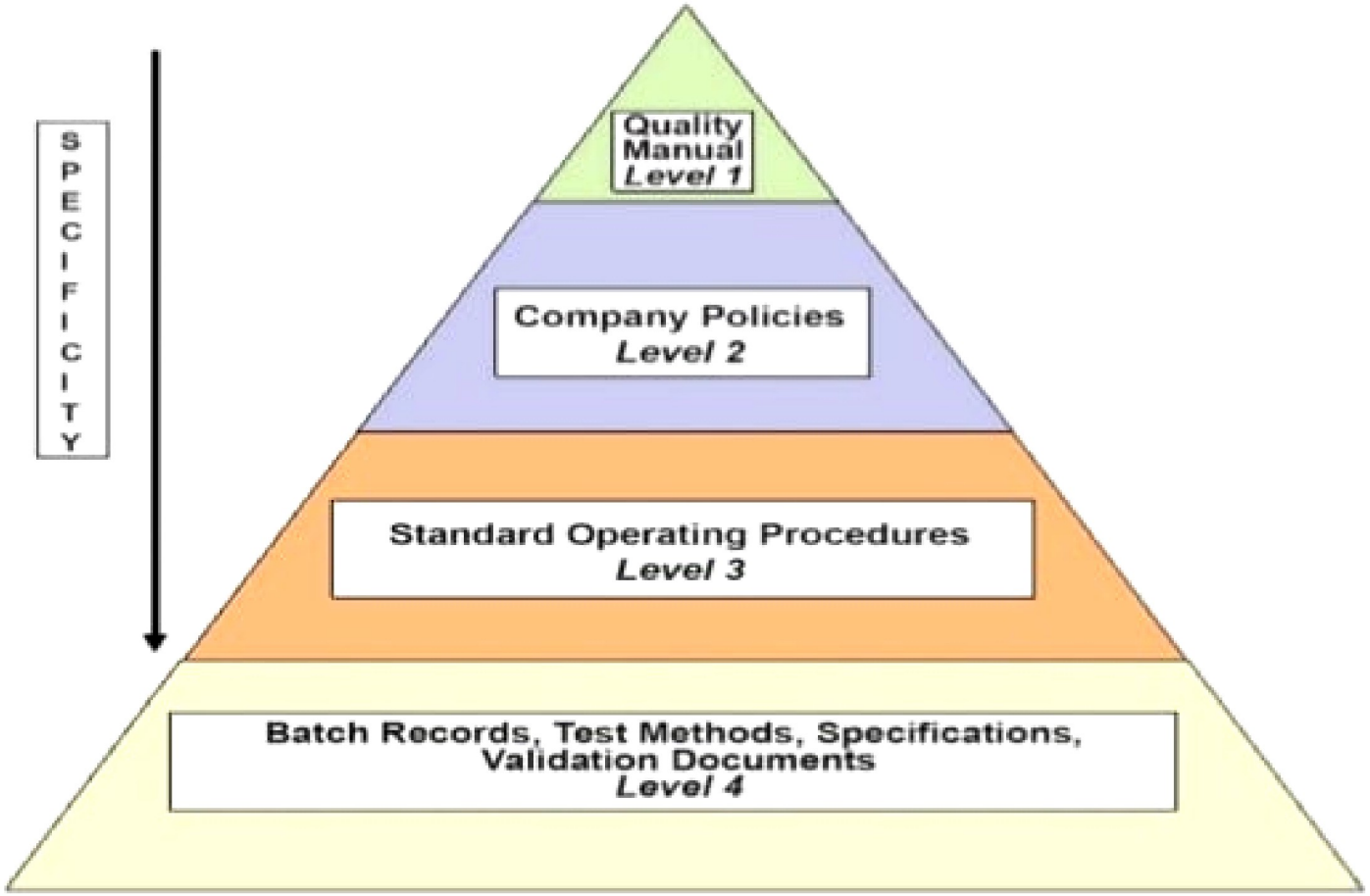
1. Get the facility design right from the start
2. Validate processes
3. Write good procedures and follow them
4. Identify who does what
5. Keep good records
6. Train and develop staff
7. Practice good hygiene
8. Maintain facilities and equipment
9. Build quality into the whole product lifecycle
10. Perform regular audits

Types of Documents

1. ***Quality manual***: A global company document that describes, in paragraph form, the regulations and/or parts of the regulations that the company is required to follow.
2. ***Policies:*** Documents that describe in general terms, and not with step-by-step instructions, how specific GMP aspects (such as security, documentation, health, and responsibilities) will be implemented.
3. ***Standard operating procedures (SOPs):*** Step-by-step instructions for performing operational tasks or activities.
4. ***Batch records:*** These documents are typically used and completed by the manufacturing department. Batch records provide step-by-step instructions for production-related tasks and activities, besides including areas on the batch record itself for documenting such tasks.

5. ***Test methods:*** These documents are typically used and completed by the quality control (QC) department. Test methods provide step-by-step instructions for testing supplies, materials, products, and other production-related tasks and activities, e.g., environmental monitoring of the GMP facility. Test methods typically contain forms that have to be filled in at the end of the procedure; this is for documenting the testing and the results of the testing.
6. ***Specifications:*** Documents that list the requirements that a supply, material, or product must meet before being released for use or sale. The QC department will compare their test results to specifications to determine if they pass the test.
7. ***Logbooks:*** Bound collection of forms used to document activities. Typically, logbooks are used for documenting the operation, maintenance, and calibration of a piece of equipment. Logbooks are also used to record critical activities, e.g., monitoring of clean rooms, solution preparation, recording of deviation, change controls and its corrective action assignment.

Hierarchical Document System



- The regulations that a company is responsible for following (e.g., USFDA/EU GMP/ICH/Schedule M, etc.) should be at the top of the document pyramid and should govern the directives of the sublevels.
- The level immediately beneath the regulations, level 1 documents (e.g., the Quality Manual), should break the regulations into parts specific to those that the company is required to follow. These documents should establish overall principles and guidelines for how the company plans on developing, documenting, and implementing a cCMP-compliant quality system. Top-level documents apply to all departments within a cGMP-compliant company and are not specific in nature.
- The next level, level 2, of documents in the hierarchical document pyramid should further break down the parts of the regulations into specific subjects or topics. These documents (e.g., Company Polices) should establish guidelines with which all subordinate level procedures must comply to ensure consistency across departments.
- Level 2 documents should not provide specific directive instructions or forms for documenting data but rather provide the overall intentions and guidelines governing critical programs or systems as well as explanation for the rationale and program designs. These documents will apply to all departments within a GMP-compliant company.

- SOPs should be the next level in the document hierarchy after company policy documents. These types of documents should provide specific step-by-step instructions for performing the operational tasks or activities that were talked about in the previous levels (for example: SOP titled 'Writing, Revising, Numbering, and Distributing Controlled Documents'). Level 3 documents (i.e., SOPs) should be department specific or function specific.
- The last level of documents in a document hierarchical structure are level 4 documents. These documents are the most specific in nature, (e.g., batch record, test methods, validation procedures). They apply to a specific department, product, equipment, or process. Level 4 documents provide step-by-step instructions for production-related tasks and activities as well as provide a means for documenting such tasks using, for example, data sheets, forms, or batch records. The details outlined in these documents may override directions given in other level documents.
- The document hierarchy pyramid is one way of organizing a company's documents.

Master Formula Record

- A document or set of documents specifying the starting material with their quantities and the packaging materials, together With a description of the procedure and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls
- Master Formula Record is also called MFR, Master Production Record. MFR is used as reference standard for preparing batch manufacturing record (BMR) by manufacturing units.
- It is prepared by the research and development team of the company. It contains all Information about the manufacturing process for the product
- Master Formula Record (MFR) is a master document for any pharmaceutical product.
- There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured.
- These shall be prepared and endorsed by the competent technical staff i.e., head of production and quality control.
- A Master Formula Record is either prepared based upon experience of impotent qualified staff like manufacturing chemist or analytical chemist or prepared based upon batch manufacturing record of a batch size.

Parts of MFR

MFR includes-

- Product Details : Name, logo and address of the manufacturing company
- Dosage form name. Brand name, Generic name.
- Product code and Label claim of all ingredients
- Product description : Batch size, Pack size and packing style
- Shelf life and Storage conditions
- MFR number and date: Supersede MFR number and date
- Effective batch number
- Authorization by the production and quality assurance head
- Equipment: A list of all required equipment and machines required in the Manufacturing process with their capacity

- Special instructions: The precautions and special instructions to be followed during the product manufacturing and packing
- Calculations: Include the calculation steps of all active materials to get the 100% of the active material. The calculation is done using water or LOD to get 100% potency
- Manufacturing Process: All steps in all stages of the manufacturing process are written. All process steps like shifting, milling, lubricating, granulation, compression and coating are written in detail including the process time and yield. It also include atmospheric conditions as temperature, humidity, and storage conditions for every step
- Packing Process: List of all packing materials with their quantity is written. Line clearance, reconciliation of printed and unprinted packing materials should be included in details
- Yield: Include the theoretical, actual yield and acceptance limit of the batch.

Steps for preparation of MFR

- Production Department prepares MFR.
- It is divided into two sections
  - Manufacturing
  - Packaging
- The first page of both the sections shall have following details:
  - Name
  - Address
  - logo of the company
  - Dosage form
  - Brand name
  - Generic name
  - Product code
  - Label claim include all ingredients and text included in product permission.
  - Product Description,
  - Shelf Life,
  - Pack Size,
  - Batch Size
  - Storage conditions.

- The secondary page of manufacturing section shall include-
  - Processes to monitor. Subsequent pages shall include the processes to be monitored.
  - The list of equipment machines, utensils to be used, shall be described.
- The subsequent page shall include any Special precautions to be taken for the product during manufacturing and packing. The same should also include Batch Manufacturing formula
- At the end of every important stage, include a statement of the yield with the acceptable Limits. In-process quality checks during and at the end of important steps and stages with their limits are included.
- The process shall include the equipment to be used.

- The methods or the reference of the methods/procedures to employed for preparing, cleaning assembling, operating the various equipments are given.
- Detailed stepwise processing instructions (example: checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures, humidity etc.) is included.
- The requirements for storage conditions of the products is also present.
- The secondary page of packaging section of MFR should include complete list of all then packaging materials required for a standard batch size including quantities sizes and types Include line clearance checking during batch cording and batch packaging operations.
- Includes reconciliation of printed and unprinted packaging materials with acceptable limits.
- Includes destruction of excess or rejected printed packaging materials Includes description of packaging Operation including any significant subsidiary operations and equipments to be used.

- https://www.who.int/immunization_standards/vaccine_quality/guide_to_master_formulae_final_2012.pdf

Drug Master Files

Introduction

- A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
- The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder.
- The information contained in the DMF may be used to support an Investigational New Drug Application (INDA), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.

- A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application.
- It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.
- DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file.

Terminology

- ***Agency*** means the Food and Drug Administration.
- ***Agent or representative*** means any person who is appointed by a DMF holder to serve as the contact for the holder.
- ***Applicant*** means any person who submits an application or abbreviated application or an amendment or supplement to them to obtain FDA approval of a new drug or an antibiotic drug and any other person who owns an approved application (21 CFR 314.3 (b)).
- ***Drug product*** means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3 (b)).
- ***Drug substance*** means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3 (b)).

- ***Export application*** means an application submitted under section 802 of the Federal Food, Drug, and Cosmetic Act to export a drug that is not approved for marketing in the United States.
- ***Holder*** means a person who owns a DMF.
- ***Letter of authorization*** means a written statement by the holder or designated agent or representative permitting FDA to refer to information in the DMF in support of another person's submission.
- ***Person*** includes individual, partnership, corporation, and association. (Section 201(e) of the Federal Food, Drug, and Cosmetic Act.)
- ***Sponsor*** means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization (21 CFR 312.3 (b)).

Types of Drug Master Files

There are five types of DMF's:

- Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel
- Type II Drug Substance, Drug Substance Intermediate, and Material used in their preparation, or Drug Product
- Type III Packaging Material
- Type IV Excipient, Colorant, Flavor, Essence, or Material used in their preparation
- Type V FDA accepted reference information

Submissions To Drug Master Files

- Each DMF submission should contain
  - a transmittal letter,
  - administrative information about the submission,
  - the specific information to be included in the DMF as described in this section

➢ **Transmittal Letters:** It should contain the following

Original Submissions

a. Identification of submission: Original, the type of DMF as classified in Section III, and its subject.

b. Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers.

c. Signature of the holder or the authorized representative.

d. Typewritten name and title of the signer.

Amendments

a. Identification of submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.

b. A description of the purpose of submission, e.g., update, revised formula, or revised process.

c. Signature of the holder or the authorized representative.

d. Typewritten name and title of the signer.

➢**Administrative Information** It should include the following

Original Submissions

a. Names and addresses of the following:
   (1) DMF holder.
   (2) Corporate headquarters.
   (3) Manufacturing/processing facility.
   (4) Contact for FDA correspondence.
   (5) Agent(s), if any.

b. The specific responsibilities of each person listed in any of the categories in Section a.

c. Statement of commitment.

A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

Amendments

a. Name of DMF holder.

b. DMF number.

c. Name and address for correspondence.

d. Affected section and/or page numbers of the DMF.

e. The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support.

f. The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for support, if known.

g. Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known.

➢Drug Master File Contents

- Types of Drug Master Files
- General Information and Suggestions
  - Environmental Assessment
  - Stability
  - Format, Assembly, and Delivery
    - An original and duplicate are to be submitted for all DMF submissions.
    - The original and duplicate copies must be collated, fully assembled, and individually jacketed
    - U.S. standard paper size (8-1/2 by 11 inches) is preferred
    - The left margin should be at least three fourths of an inch
    - Delivery to FDA

Authorization to refer to a Drug Master File

- **Letter of Authorization to FDA**
  - Before FDA can review DMF information in support of an application, the DMF holder must submit in duplicate to the DMF a letter of authorization permitting FDA to reference the DMF.
  - If the holder cross references its own DMF, the holder should supply in a letter of authorization
  - The holder does not need to send a transmittal letter with its letter of authorization.
  - The letter of authorization should include the following:
    - The date.
    - Name of DMF holder.
    - DMF number.
    - Name of person(s) authorized to incorporate information in the DMF by reference.
    - Specific product(s) covered by the DMF.
    - Submission date(s) of 5, above.
    - Section numbers and/or page numbers to be referenced.
    - Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.
    - Signature of authorizing official.
    - Typed name and title of official authorizing reference to the DMF.
- **Copy to Applicant, Sponsor, or Other Holder**

Processing And Reviewing Policies

- Policies Related to Processing Drug Master Files
  - Public availability of the information and data in a DMF is determined under 21 CFR Part 20, 21 CFR 314.420(e), and 21 CFR 314.430.
  - An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number.
- Drug Master File Review

Holder Obligations

- Notice required for changes to a drug master file
- Listing of persons authorized to refer to a drug master file
- Annual update
- Appointment of an agent
- Transfer of ownership

Major Reorganization of a Drug Master File

- A holder who plans a major reorganization of a DMF is encouraged to submit a detailed plan of the proposed changes and request its review by the Drug Master File Staff.
- The staff should be given sufficient time to comment and provide suggestions before a major reorganization is undertaken.

Closure of a Drug Master File

- A holder who wishes to close a DMF should submit a request to the Drug Master File Staff stating the reason for the closure. See Section IV.D.5.a for the address.
- The request should include a statement that the holder's obligations as detailed in Section VII have been fulfilled.
- The Agency may close a DMF that does not contain an annual update of persons authorized to incorporate information in the DMF by reference and a list of changes made since the previous annual report. The holder will be notified of FDA's intent to close the DMF.

- https://www.fda.gov/drugs/guidances-drugs/drug-master-files-guidelines

Distribution Records

- Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.
- The primary purpose is to ensure that adequate data are available to access trade customers should a recall be initiated. The recording of lot number to each order will certainly accomplish this purpose.
- Distribution records must be constructed and procedures established to facilitate recall of defective product.
- Distribution records include a wide range of documentation such as invoices, bills of lading, customers' receipts, internal warehouse storage and inventory records.
- The information required need not be on every document. Also customer codes and product codes may be used as alternates to customer names and address and product names.

Generic Drug Product Development

- A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

- Generic drug product manufacturers must formulate a drug product that will have the same therapeutic efficacy and clinical performance as their brand-name counterpart.

SELECTION OF GENERIC DRUGS

- The main driving force for the selection of generic drug products for manufacture is the estimated sales volume for the branded product.
- Also, the potential market share that the firm expects to have once the generic drug product is manufactured and approved for marketing.
- In addition to the expiration date of the patent for the active ingredient, the generic firm must consider any other patent claims and exclusivities that the innovator firm has filed.

GENERIC DRUG APPROVAL PROCESS

- The FDA's office of Generic Drugs is responsible for reviewing the ANDA and approving the drug products marketing.
- The FDA's Office of Generic drugs has a website https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-generic-drugs that provides additional information for manufactures of generic drug products
- And it also describes how FDA determines the quality, safety, and efficacy of generic drug products prior to the approval for marketing.
- Generic drug application reviewers focus on bioequivalence data, chemistry and manufacture quality, microbiology data where relevant, requests for plant inspection, and drug labeling information

- The ANDA for generic drug product approval is based on bioequivalence to the brand name product, appropriate chemistry and manufacturing information, and appropriate labeling.
- Generic drug sponsors do not have to perform the nonclinical animal toxicity studies or expensive clinical efficacy and safety studies that are included in the new drug application.
- NDA which is submitted to the FDA for market approval of the brand name drug product.
- The ANDA contains data which is then submitted to FDA's Center for drug evaluation and research for the generic drugs.

- FDA approved generic drugs must meet the same rigid standards as the innovator drug.
- To obtain FDA approval, a generic drug product must-contain same active ingredient as an approved drug product the inactive ingredients may vary.

- https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/generic-drug-development

Abbreviated New Drug Application (ANDA)

- An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product.
- Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references.
- All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
- Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

- Instead, generic applicants must scientifically demonstrate that their product is performs in the same manner as the innovator drug.
- For the generic drug to be therapeutically equivalent, two clinical characteristics must apply:
  - It must be pharmaceutically equivalent as well as bioequivalent.
  - Pharmaceutical equivalence means that the active ingredient(s), dose form, route of administration, and strength are the same for both the branded product and the generic product.
  - Bioequivalence is when both products have comparable bioavailability when studied under similar conditions.
- To be approved by FDA, the generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.
- The "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Hatch-Waxman Amendments, established bioequivalence as the basis for approving generic copies of drug products.

- **Resources for ANDA Submissions**
  - Summary tables, application forms, and other ANDA submission resources are available in

https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/abbreviated-new-drug-application-anda-forms-and-submission-requirements

- **Guidance Documents for ANDAs**
  - These documents provide guidelines for the content, evaluation, and ultimate approval of applications and also to the design, production, manufacturing, and testing of regulated products for FDA review staff, applicants, and ANDA holders.
    - Generic Drugs Guidances (Search "Generics" under topics)
    - Biopharmaceutics Guidances (Search "Biopharmaceutics" under topics)
    - Product-Specific Guidances for Generic Drug Development

- **Laws, Regulations, Policies, and Procedures**
  - *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the United States.
  - The law is intended to assure consumers
    - that foods are pure and wholesome, safe to eat, and produced under sanitary conditions;
    - that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients;
    - and that all labeling and packaging is truthful, informative, and not deceptive.

- **Code of Federal Regulations**
- The *Code of Federal Regulations* (CFR) is the official legal print publication containing the codification of the general and permanent rules published in the *Federal Register* by the departments and agencies of the Federal Government.
- The Electronic Code of Federal Regulations (eCFR) is a continuously updated online version of the CFR. It is not an official legal edition of the CFR.
- The final regulations published in the Federal Register (a daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code of Federal Regulations (CFR).
- Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug applicants that are required under Federal law.
- The following regulations directly apply to the ANDA process:
  - 21CFR Part 314: Applications for FDA Approval to Market a New Drug
  - 21CFR Part 320: Bioavailability and Bioequivalence Requirements
- https://www.ecfr.gov/

- **Manual of Policies and Procedures**
  - CDER's Manual of Policies and Procedure (MAPPs) document internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external.
  - Chapter 5200 covers generic drugs processes and activities.

https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda

HATCH-WAXMAN ACT AND AMENDMENTS

- **The Hatch-Waxman Act (formally known as the Drug Price Competition and Patent Term Restoration Act)** is a law passed in 1984 that created the generic drug industry
- Hatch-Waxman Amendments, established the approval pathway for generic drug products, under which applicants can submit an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
- The Hatch-Waxman Amendments include provisions that involve patents and exclusivities related to new drug applications, and 180-day exclusivity for certain ANDA applicants.

- Amended the patent laws
  - Before 1962- new drug approval based on safety alone
  - In 1962-proof of efficacy made compulsory for marketing approval of a new drug
- There was no provision for patent term extension prior to enactment of the hatch-waxman act to make up for the time lost out of the total patent term during the marketing approval process
- Generic companies were required to submit their own comprehensive NDA which were costly & time consuming.
- To overcome the above problems, an act was needed to promote generic companies

OBJECTIVES OF THE ACT

- Reducing the cost associated with the approval of a generic drug
- Allowing early-experimental use
- Compensating the branded drugs manufacturers for the time lost from the patent term because of the regulatory approval formality
- Motivating the generic drug manufacturers

DRUG APPROVAL

- The FDA requires every new drug, including generic drugs, to be safe and effective.
- Before the adoption of the Hatch- Waxman Act, the FDA required branded and generic drug companies alike to demonstrate the safety and efficacy of their products in the same manner through a New Drug Application (NDA)
- The Hatch-Waxman Act changed certain aspects of the new drug application process and the new drug's patent term.
- In addition, the Hatch-Waxman Act created an abbreviated process to allow generic drug companies to obtain FDA approval of generic drugs. Because of this, today it is far easier for generic drug companies to demonstrate the safety and efficacy of their generic drugs

- Under the Hatch-Waxman Act, generic drug companies can typically file one of two different kinds of abbreviated applications for approval of a generic drug:
  - An Abbreviated New Drug Application (ANDA)
  - A Section 505(b)(2) application, which is often called a paper NDA
- Section 505(b)(2) Applications
  - A proposed generic drug may differ in significant ways from the RLD,
  - Under these circumstances, the proposed generic drug must be approved through the Section 505(b)(2) paper NDA application process, which is a hybrid of a full NDA and an ANDA. This application includes less data than an NDA but more data than an ANDA.

PATENT TERM EXTENSION

- The Hatch-Waxman Act provides a patent term extension for patents covering certain products and methods, including human drug products, that are subject to FDA approval.
- Only one extension can be granted in connection with a particular product, and it must be for a patent that claims either
  - Drug product, which means the active ingredient and any approved drug using that active ingredient.
  - Method of using a drug product.
  - Method of manufacturing a drug product

NEW DRUG EXCLUSIVITY

- Non-patent Exclusivities
  - Orphan drug exclusivity, which is granted to drugs:
    - that treat a disease or condition that affects less than 200,000 people in the US; or
    - for which it is unlikely that US sales of the drug will recoup its development costs.
    - This exclusivity period is seven years, but only applies to use in treating the specific rare disease or condition
    - Term is 7 years
  - New chemical entity (NCE) exclusivity
    - This is granted if the FDA has not previously approved the "active drug moiety."
    - NCE exclusivity bars a generic drug company from filing an application for approval of a generic drug five years from the first approval of the relevant NDA.
    - However, a generic drug company may file an ANDA with a Paragraph IV certification four years after the first NDA approval
    - Term is 5 years

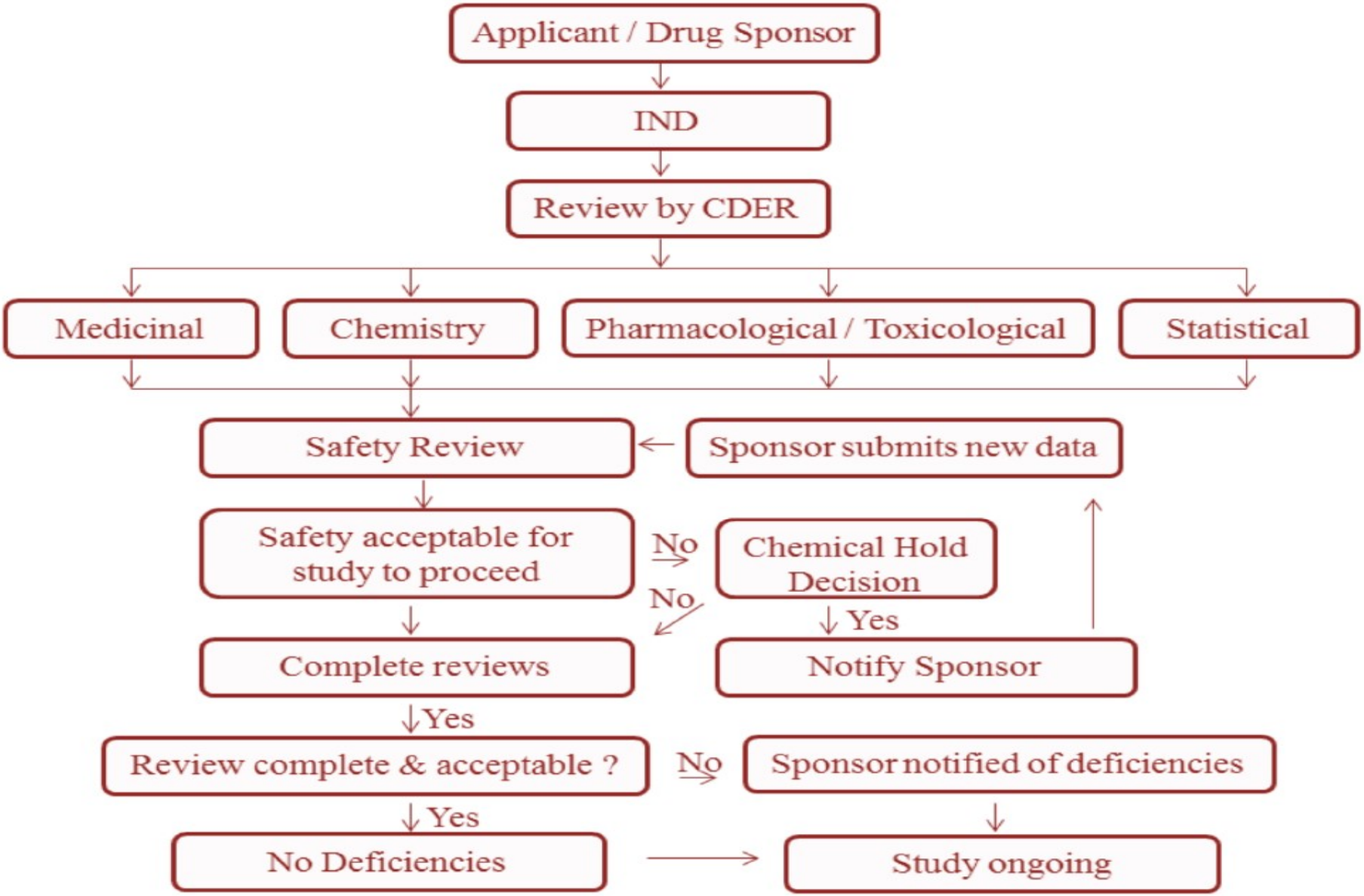
- New clinical study exclusivity
  - This applies when new clinical studies lead to new or changed formulations, dosing regimens or patient population.
  - The applicant is entitled to this exclusivity if an application or supplement contains reports of new clinical investigations conducted or sponsored by the applicant that were essential for approval.
  - This exclusivity, sometimes called data exclusivity, prohibits the FDA from approving a generic drug application for the new dosage form or use for three years after the first NDA approval.
  - However, it does not otherwise bar approval of generic drug applications
  - Term is 3 years
- Pediatric exclusivity
  - This applies if the FDA requested that the NDA holder conduct studies with the drug in pediatric populations.
  - Pediatric exclusivity adds six months of exclusivity to any marketing or patent exclusivity
  - Term is 6 months

- Patent exclusivity
  - An NDA holder must provide the FDA with the patent number and expiration date of any patent that claims either:
    - The drug, including the active ingredient and the formulation for the active ingredient.
    - A method of using the drug, but not other inventions such as:
      - metabolites;
      - synthetic intermediates; or
      - methods of making the drug.
  - When the FDA approves the NDA, the FDA publishes the patent information in the FDA's Approved Drug Products with Therapeutic Equivalence Determinations publication (also called the Orange book)

Principles & Procedures For New Drug Applications

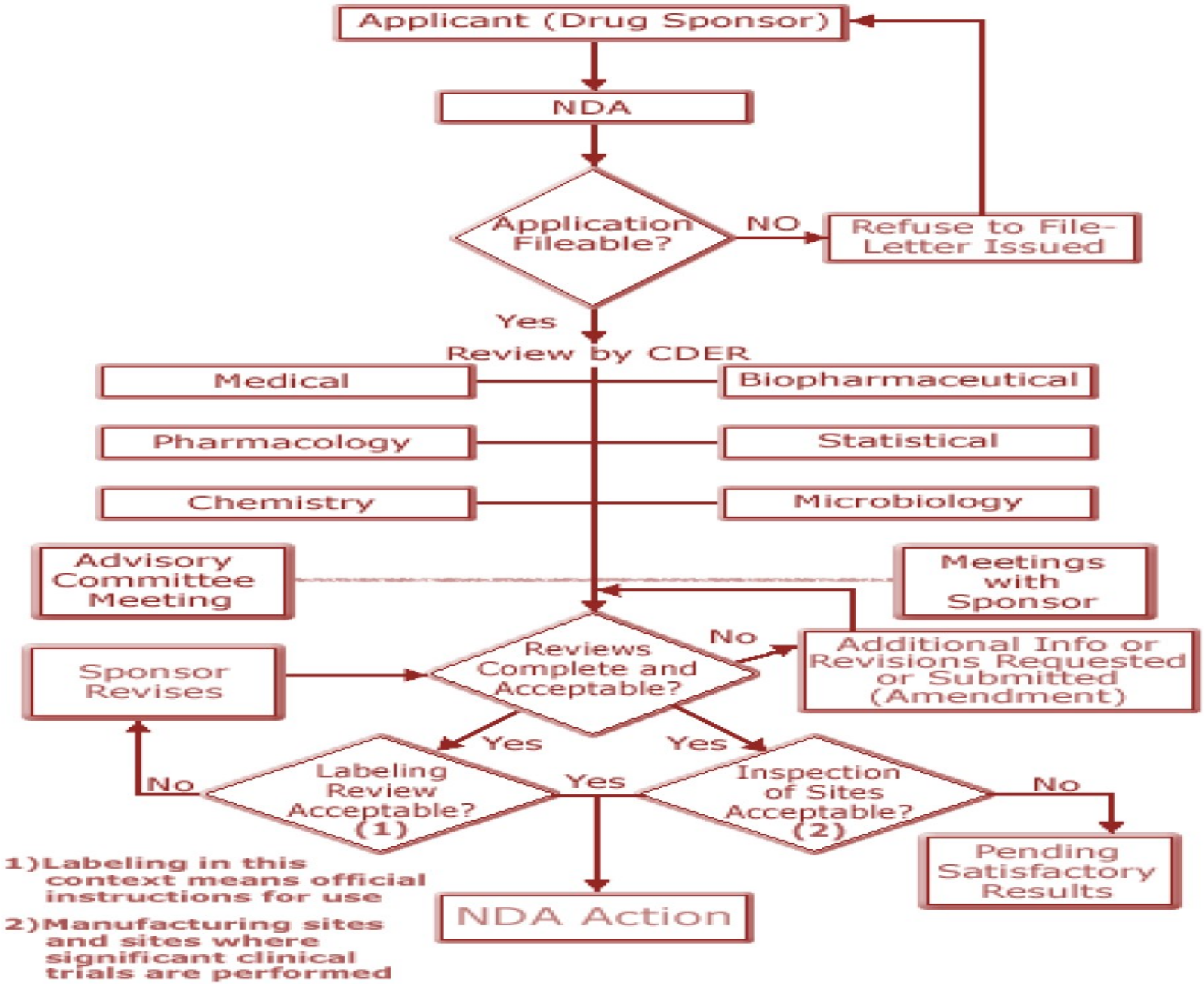
- The FDA new drug approval process begins with research plans involving basic research, laboratory, and animal testing.
- This initial stage includes discovery and development of prototypes involving preclinical and clinical studies of new drug materials to be reviewed and approved by an institutional review board (IRB).
- The FDA filing and premarket applications consist of the following categories:
  - Investigational New Drug Application (IND)
  - New Drug Application (NDA)
  - Abbreviated New Drug Application (ANDA)

- **Investigational New Drug Application (IND)**
  - It's 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.
  - 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.

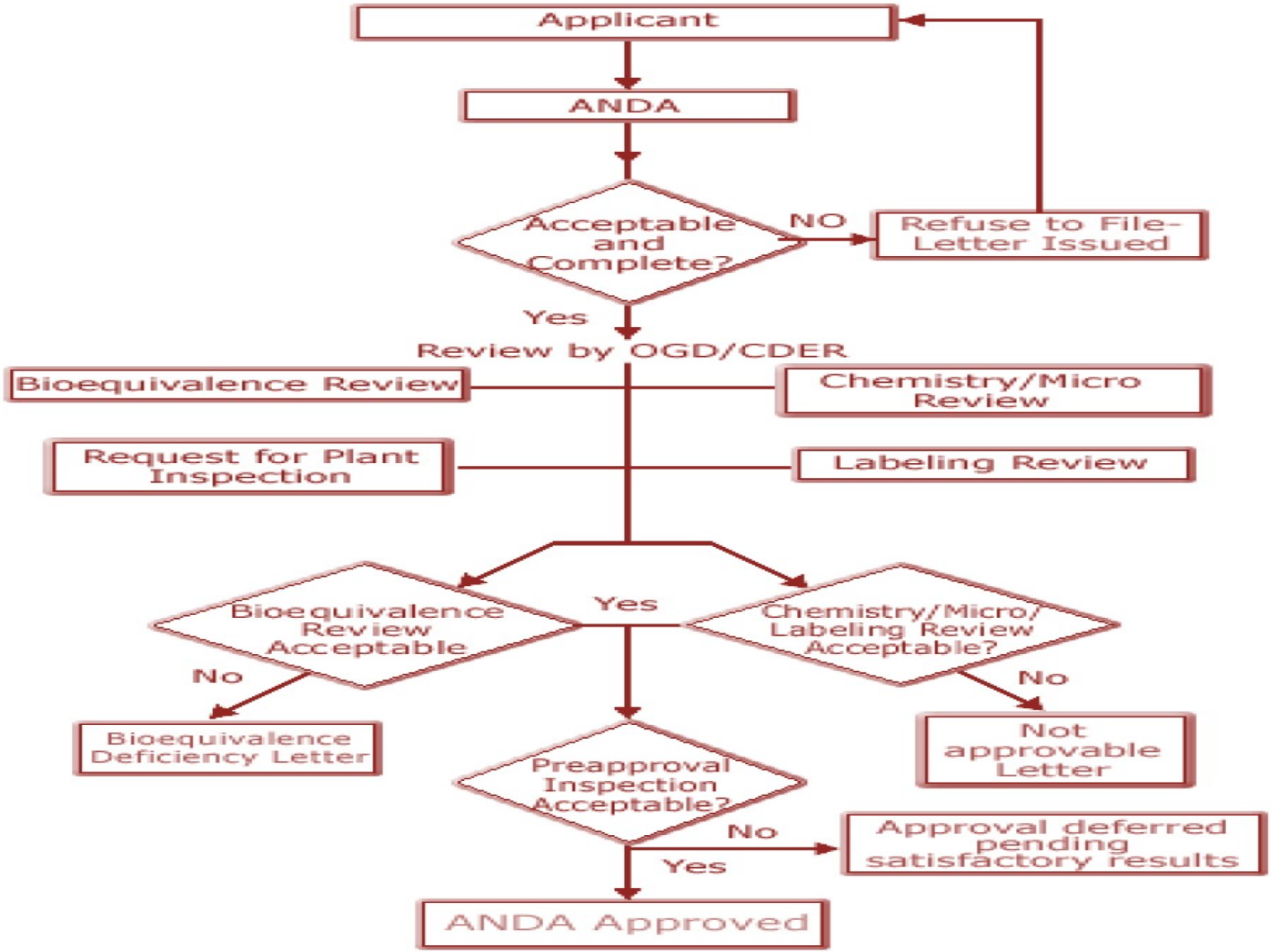


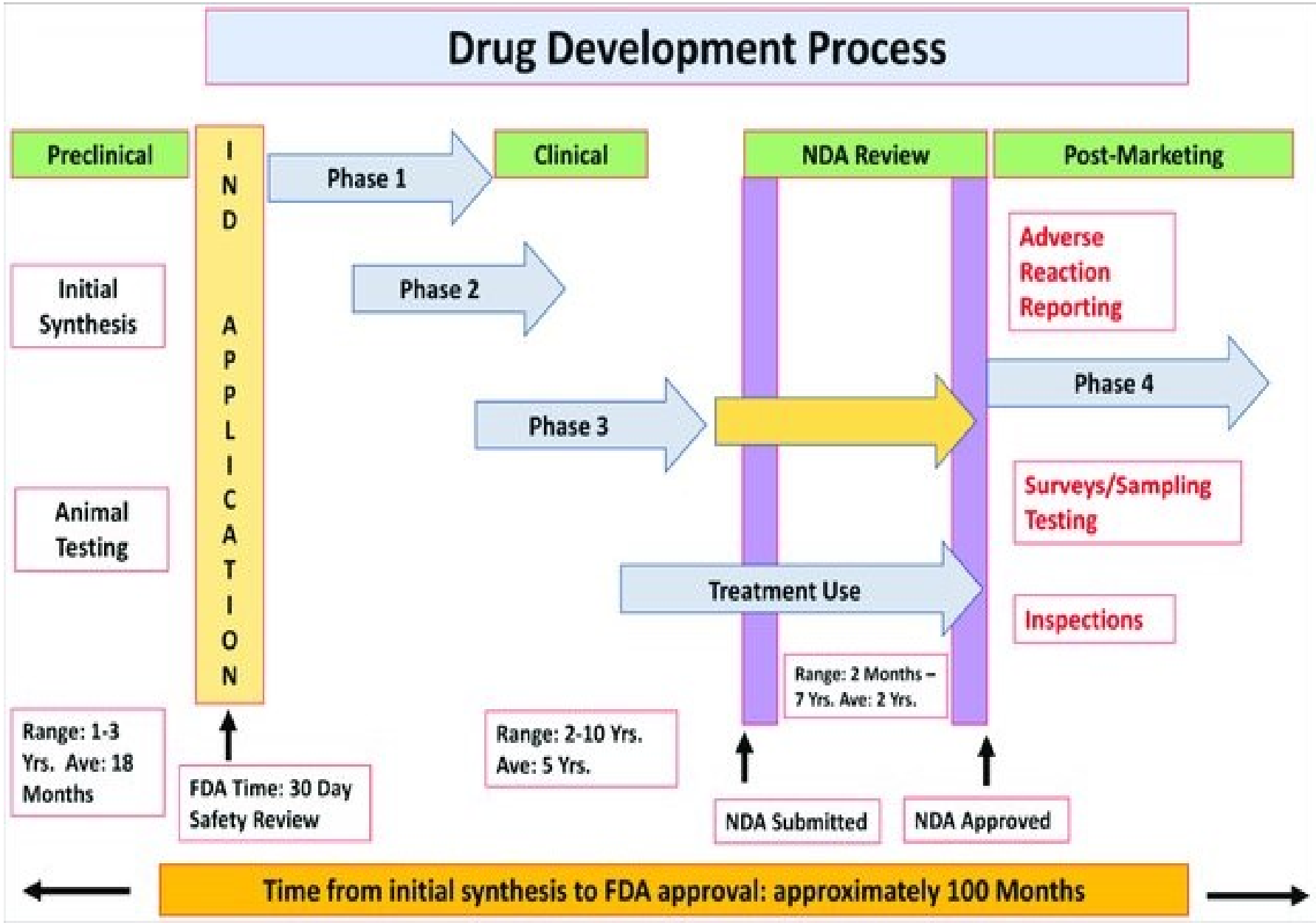
Investigational New Drug Application (IND)

- **New Drug Application (NDA)**
  - NDA is an application submitted to the FDA for permission to market a new drug.
  - To obtain this permission a sponsor submits preclinical and clinical test data to NDA for analyzing the drug information, description of manufacturing procedures.
  - After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application that is FDA formal review.
  - At the conclusion of FDA review of an NDA, there are 3 possible actions that can send to sponsor:
    - Not approvable- in this letter list of deficiencies and explain the reason.
    - 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.
    - Approval- it state that the drug is approved.


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
No
Labeling Review Acceptable? (1)
Yes
Inspection of Sites Acceptable? (2)
No
Pending Satisfactory Results
NDA Action
1)Labeling in this context means official instructions for use
2)Manufacturing sites and sites where significant clinical trials are performed

- **Abbreviated New Drug Application (ANDA)**
- It's an application made for approval of Generic Drugs.
- The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product.
- Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product


Applicant
ANDA
Acceptable and Complete?
NO
Refuse to File– Letter Issued
Yes
Review by OGD/CDER
Bioequivalence Review
Chemistry/Micro Review
Request for Plant Inspection
Labeling Review
Bioequivalence Review Acceptable
Yes
Chemistry/Micro/ Labeling Review Acceptable?
No
No
Bioequivalence Deficiency Letter
Not approvable Letter
Preapproval Inspection Acceptable?
No
Approval deferred pending satisfactory results
Yes
ANDA Approved


Drug Development Process
Preclinical
IND APPLICATION
Clinical
NDA Review
Post-Marketing
Phase 1
Phase 2
Phase 3
Phase 4
Initial Synthesis
Animal Testing
Adverse Reaction Reporting
Surveys/Sampling Testing
Inspections
Treatment Use
Range: 1-3 Yrs. Ave: 18 Months
FDA Time: 30 Day Safety Review
Range: 2-10 Yrs. Ave: 5 Yrs.
Range: 2 Months – 7 Yrs. Ave: 2 Yrs.
NDA Submitted
NDA Approved
Time from initial synthesis to FDA approval: approximately 100 Months

In Vitro Drug Product Performance

- Dissolution and drug release tests are *in vitro* tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually in an aqueous medium under specified conditions.
- *In vitro* dissolution testing provides useful information throughout the drug development process
- The dissolution test is an important quality control procedure used to confirm batch-to-batch reproducibility and to show typical variability in composition and manufacturing parameters.
- Dissolution and drug release tests are also used as a measure of drug product performance, *in vitro* when linked to product performance *in vivo*.
- Ideally, the dissolution method used for a particular drug product *in vitro* should mimic the release characteristics of the drug product *in* vivo and should potentially be able to differentiate among formulations with different release characteristics.

- The ultimate goal is to identify a dissolution test that is capable of distinguishing between acceptable and unacceptable drug formulations as observed by different drug dissolution rates under the same experimental conditions.
- Overall, a suitable dissolution test should be able to reflect changes in the formulation, manufacturing process, and physical and chemical characteristics of the drug, such as particle size, polymorphs, and surface area
- The dissolution test is typically a requirement for routine batch testing and qualification of certain scale-up and post-approval changes (SUPAC) for many marketed drug products
- If the changes are deemed minor, the impact on its *in vivo* performance can be assessed by comparing the pre- and postchange product dissolution profile using the approved dissolution method or under different pH conditions.
- Major post-approval manufacturing changes require a bioequivalence study to support approval of the change, but this bioequivalence study may be waived in the presence of an acceptable *in vitro–in vivo correlation*

- the dissolution test should be sufficiently rugged and reproducible for day-to-day operation and capable of being transferred between laboratories.

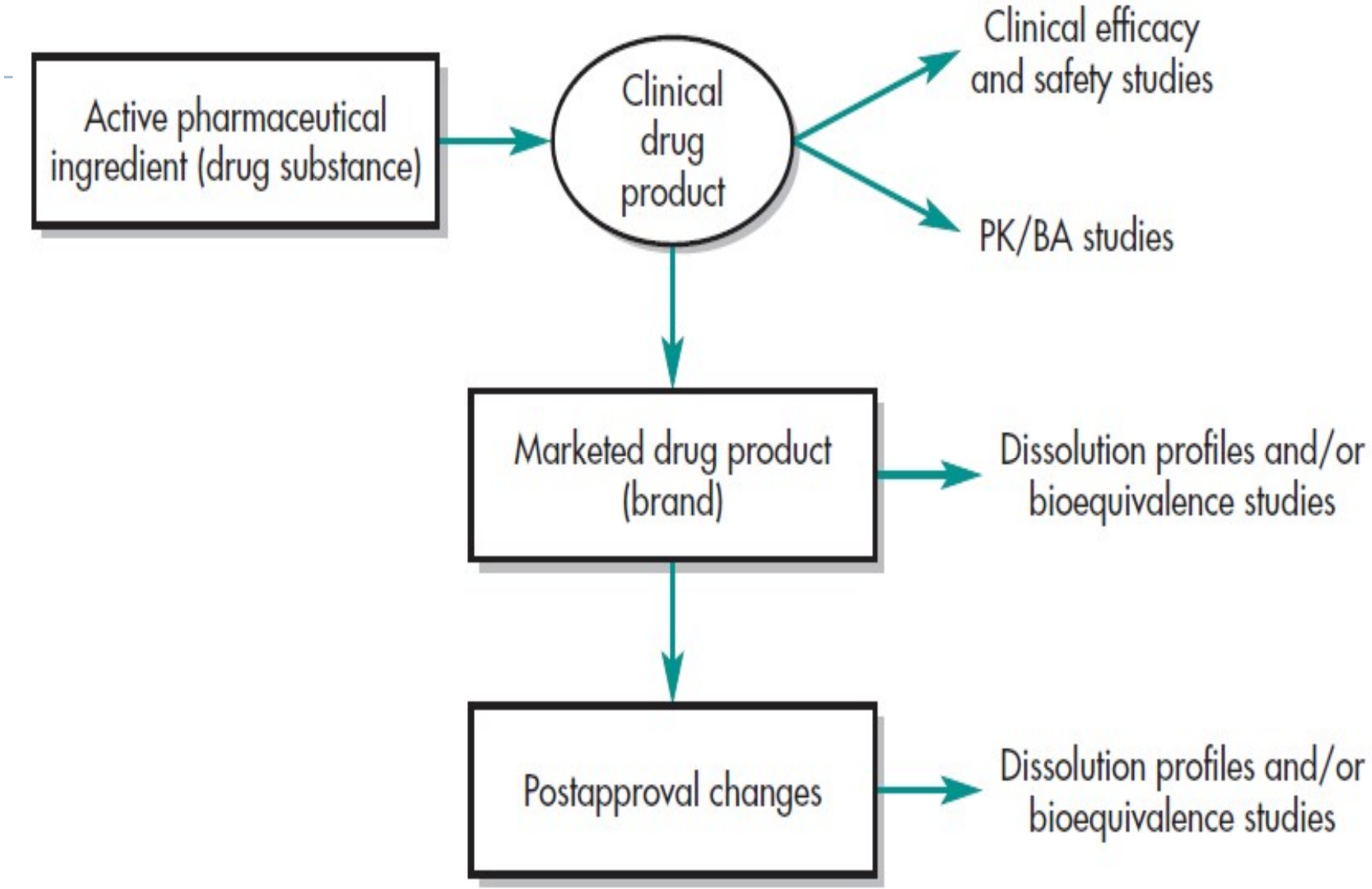
Drug Product Performance, *in vivo*

- Drug product performance, *in vivo*, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance.
- The assessment of drug product performance is important since bioavailability is related to the pharmacodynamic response and related adverse events.
- Thus, performance tests relate the quality of a drug product to clinical safety and efficacy
- Bioavailability and bioequivalence can be considered as measures of the drug product performance *in vivo*
- Drug product performance studies are used in the development of new and generic drug products

- ***Bioavailability*** studies are drug product performance studies used to define the effect of changes in the physicochemical properties of the drug substance, the formulation of the drug, and the manufacture process of the drug product (dosage form). Bioavailability is one aspect of drug product quality that links the *in vivo* performance of a new drug product to the original formulation that was used in clinical safety and efficacy studies.
- ***Bioequivalence*** studies are drug product performance tests that compare the bioavailability of the same active pharmaceutical ingredient from one drug product (test) to a second drug product (reference).
- **Equivalent drug product performance** is generally demonstrated by an *in vivo* bioequivalence study in normal healthy volunteers. Under certain conditions, equivalent drug product performance may be demonstrated *in vitro* using comparative dissolution profiles

Bioequivalence Studies in New Drug Development (NDA)

- During drug development, bioequivalence studies are used to compare
  - (a) early and late clinical trial formulations;
  - (b) formulations used in clinical trials and stability studies, if different;
  - (c) clinical trial formulations and to-be-marketed drug products, if different; and
  - (d) product strength equivalence, as appropriate
- Bioequivalence study designs are used to support new formulations of previously approved products, such as a new fixed-dose combination version of two products approved for co-administration, or modified-release versions of immediate-release products.
- Post-approval, *in vivo* bioequivalence studies may be needed to support regulatory approval of major changes in formulation, manufacturing, or site, in comparison to reference formulation

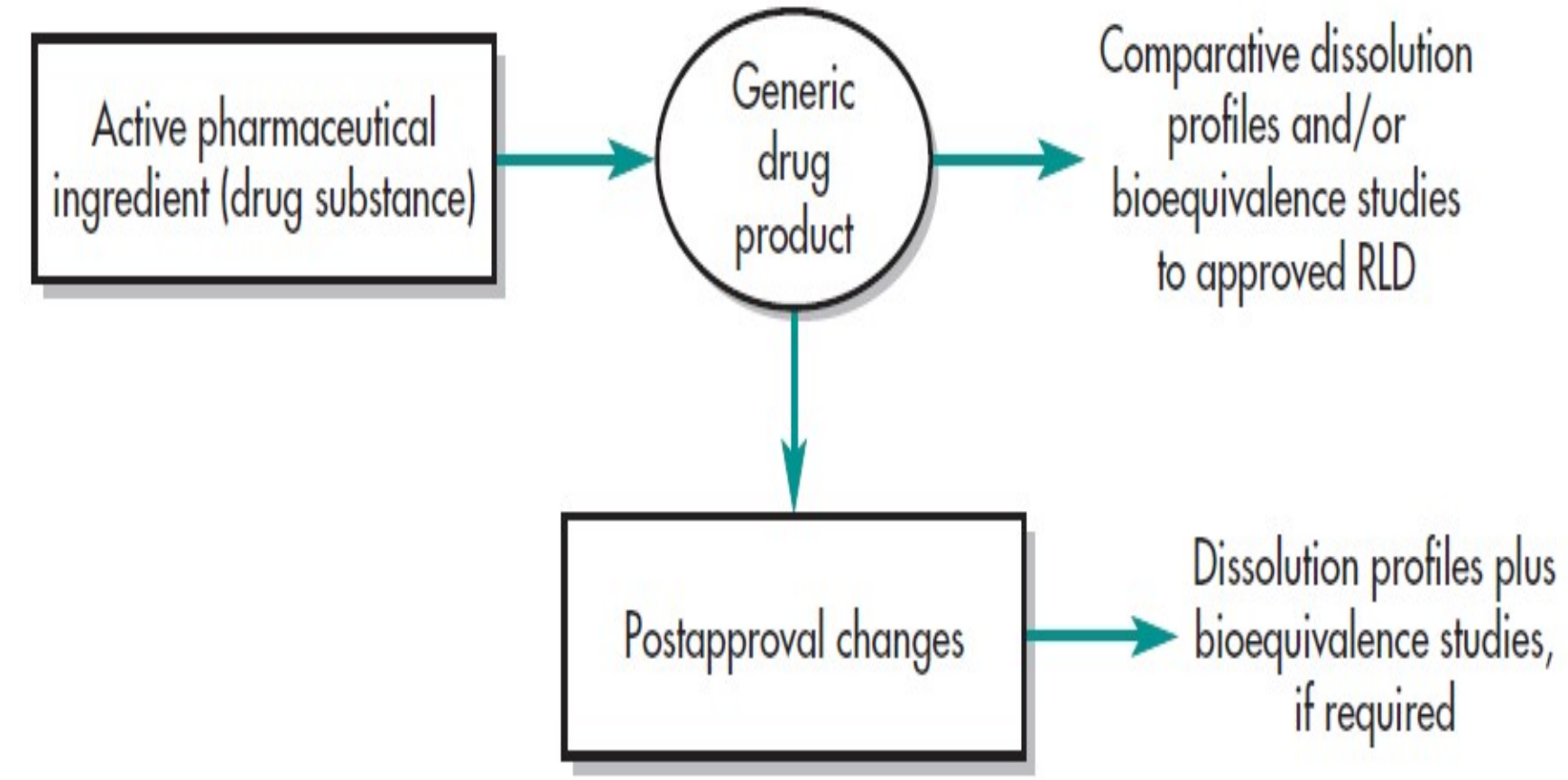

Active pharmaceutical ingredient (drug substance)
Clinical drug product
Clinical efficacy and safety studies
PK/BA studies
Marketed drug product (brand)
Dissolution profiles and/or bioequivalence studies
Postapproval changes
Dissolution profiles and/or bioequivalence studies

- The marketed drug product that is approved by the US Food and Drug Administration (FDA) may not be the same formulation that was used in the original safety and clinical efficacy studies.
- After the drug product is approved by the FDA and marketed, the manufacturer may perform changes to the formulation. These changes to the marketed drug product are known as postapproval changes
- These postapproval changes, often termed SUPAC could include a change in the supplier of the active ingredient, a change in the formulation, a change in the manufacturing process, and/or a change in the manufacturing site
- In each case, the manufacturer must demonstrate that drug product performance did not change and is the same for the drug product manufactured before and after the SUPAC change

Bioequivalence Studies in Generic Drug Development (ANDA)

- Comparative drug product performance studies are important in the development of generic drug products
- Clinical safety and efficacy studies are not generally performed on generic drug products.
- Since the formulation and method of manufacture of a drug product can affect the bioavailability and stability of the drug, the generic drug manufacturer must demonstrate that the generic drug product is pharmaceutically equivalent, bioequivalent, and therapeutically equivalent to the comparator brand-name drug product.
- Drug product performance comparison for oral generic drug products is usually measured by in vivo bioequivalence studies in normal healthy adult subjects under fasted and fed conditions.

- Drug product performance comparisons *in vitro* may also include comparative drug dissolution/release profiles.
- Similar to the brand-name drug product manufacturer, the generic drug manufacturer may make changes after FDA approval in the formulation, in the source of the active pharmaceutical ingredient, manufacturing process, or other changes.
- For any postapproval change, the manufacturer must demonstrate that the change did not alter the performance of the drug product.


Active pharmaceutical ingredient (drug substance)
Generic drug product
Comparative dissolution profiles and/or bioequivalence studies to approved RLD
Postapproval changes
Dissolution profiles plus bioequivalence studies, if required

Methods for Assessing Bioavailability and Bioequivalence

- ***In vivo measurement of active moiety or moieties in biological fluids***
  - **Plasma drug concentration**
    - Time for peak plasma (blood) concentration (*tmax)*
    - Peak plasma drug concentration (*Cmax)*
    - Area under the plasma drug concentration–time curve (AUC)
  - **Urinary drug excretion**
    - Cumulative amount of drug excreted in the urine (*Du)*
    - Rate of drug excretion in the urine (*dDu/dt)*
    - Time for maximum urinary excretion (*t)*

- ***In vivo pharmacodynamic (PD) comparison***
  - Maximum pharmacodynamic effect (*Emax)*
  - Time for maximum pharmacodynamic effect
  - Area under the pharmacodynamic effect–time curve
  - Onset time for pharmacodynamic effect
- **Clinical endpoint study**
  - Limited, comparative, parallel clinical study using predetermined clinical endpoint(s) and performed in patients
- ***In vitro studies***
  - Comparative drug dissolution, *f2 similarity factor*
  - *In vitro binding studies*
- **Any other approach deemed acceptable (by the FDA)**
  - *in vitro biomarkers*
  - *in vitro binding studies*

Regulatory Recommendations for Optimizing Bioavailability Study Design

- The FDA lists a number of recommendations to consider in designing clinical relative bioavailability studies in drug development.
- These recommendations include the following:
  - Use of a randomized crossover design whenever possible
  - Enrolling both male and female subjects whenever possible
  - Administering single doses rather than multiple doses, as single-dose studies are more sensitive, although multiple-dose studies may be more suitable in some cases
  - Conducting the studies under fasting and fed conditions6
  - Measuring the parent drug rather than metabolites, unless the parent cannot be reliably measured. Presystemically formed metabolites that contribute meaningfully to safety and efficacy should also be measured
- In addition, the FDA recommends that *Cmax and tmax be measured to compare peak exposure and rate of absorption, and that AUC0-t (AUC to the last measurable drug concentration) and AUC0-∞ (AUC extrapolated to infinity) be measured to compare total exposure or extent of drug absorption. Drug exposure parameters should be log-transformed before statistical comparisons.*

SCALE-UP AND POSTAPPROVAL CHANGES (SUPAC)

- A postapproval change is any change in a drug product after it has been approved for marketing by the FDA.
- Since safety and efficacy are established using clinical batches, the same level of quality must be ensured in the finished drug product released to the public. A change to a marketed drug product can be initiated for a number of reasons, including a revised market forecast, change in an API source, change in excipients, optimization of the manufacturing process, and upgrade of the packaging system.
- A change within a given parameter can have varied effect depending on the type of product.
- For example, a change in the container closure/system of a solid oral dosage form may have little impact on an oral tablet dosage form unless the primary packaging component is critical to the shelf life of the finished product

- If a pharmaceutical manufacturer makes any change in the drug formulation, scales up the formulation to a larger batch size, or changes the process, equipment, or manufacturing site, the manufacturer should consider whether any of these changes will affect the identity, strength, purity, quality, safety, and efficacy of the approved drug product.
- Moreover, any changes in the raw material (ie, active pharmaceutical ingredient), excipients (including a change in grade or supplier), or packaging (including container closure system) should also be shown not to affect the quality of the drug product.
- The manufacturer should assess the effect of the change on the identity, strength (eg, assay, content uniformity), quality (eg, physical, chemical, and biological properties), purity (eg, impurities and degradation products), or potency (eg, biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

- The FDA has published several SUPAC guidances, including Changes to an Approved NDA or ANDA for the pharmaceutical industry.
- These guidances address the following issues:
  - Components and composition of the drug product
  - Manufacturing site change
  - Scale-up of drug product
  - Manufacturing equipment
  - Manufacturing process
  - Packaging
  - Active pharmaceutical ingredient

- These documents describe

  (1) the level of change,

  (2) recommended CMC tests for each level of change,

  (3) in vitro dissolution tests and/or bioequivalence tests for each level of change, and

  (4) documentation that should support the change.

- The levels of change as described by the FDA are listed

Change Level	**Definition of Level**
Level 1	Changes that are unlikely to have any detectable impact on the formulation quality and performance.
Level 2	Changes that could have a significant impact on formulation quality and performance.
Level 3	Changes that are likely to have a significant impact on formulation quality and performance.

POSTMARKETING SURVEILLANCE

- Pharmaceutical manufacturers are required to file periodic postmarket reports for an approved ANDA to the FDA through its Postmarketing Surveillance Program.
- The main component of the requirement is the reporting of adverse drug experiences.
- This is accomplished by reassessing drug risks based on data learned after the drug is marketed.
- In addition, labeling changes may occur after market approval.
- For example, a new adverse reaction discussed by postmarketing surveillance is required for both branded and generic drug products.

OUTSOURCING BIOAVAILABILITY AND BIOEQUIVALENCE TO CRO

- **Outsourcing** is the business practice of hiring a party outside a company to perform services and create goods that traditionally were performed in-house by the company's own employees and staff.
- **Contract research organization (CRO)** is an entity that extends support to pharmaceutical, biotechnology and medical devices industry in the form of research services outsourced on a contract basis.
- Outsourcing is generally done to reduce the costs and improving the efficient resources within a company.
- Example of outsourcing is bioavailability, bioequivalence, R & D department etc.
- A CRO may offer such services like: Biopharmaceutical development, Clinical & preclinical research, Clinical trial, Pharmacovigilance, Biological assay development.

GOAL

- Contract research organization(CRO) provides much needed service to the pharmaceutical sector. Full service CROs offer a comprehensive selection of capabilities, while smaller "niche" CROs may focus on a narrow segment of services (clinical or analytical only).
- All of these organization fulfill a need in that they provide the services necessary for the approval of new clinical entities or generic drug products. A sampling of these services is included

Reasons of outsourcing

- Many of the large pharmaceutical companies have in- house capacity but some of which lack of in-house capacity, skill deficiency and cost control.
- Unlike their larger counter parts, the smaller companies, virtual firms and generic companies do not have the luxury of their own dedicated clinical unit or full in-house capabilities and are required to outsource their clinical trials, including bioavailability (BA) and bioequivalence (BE) studies.
- Although generic companies have internal resources for product development, manufacturing and release testing, they do not have clinical and bio analytical capabilities.

Identification of appropriate CROs

- It is important that your CRO has validated corporate procedures for all segments of clinical study conduct.
- These procedures are used to ensure that all aspects of a study, including but not limited to clinical conduct, laboratory analysis, data management, biostatistics, pharmacokinetics, and medical writing, are performed in compliance with Good Clinical Practices (GCP),Good Laboratory Practices (GLP), and other applicable regulatory practices and guidelines.

Assessment of Capabilities

1. Clinical capabilities
2. Bio analytical capabilities
3. Pharmacokinetic capabilities
4. Timeline assessment

CRO Qualification

- Due diligence
  - If the pharmaceutical firm has used the CRO in the past, they should objectively evaluate their past experience with this CRO.
  - If the experience was good, the firm should identify those components that were successful and insure that they are used for their new study.
  - However, caution should be exercised and due diligence pursed if the new study requires a different subject population or analytical technique.
  - Example: A CRO may specialize in recruiting healthy male and female volunteers, but may have difficulty in the recruitment of postmenopausal females.

- Clinical site qualification
  - The sponsor should conduct a site qualification visit. In addition to a eGCP site audit, this evaluation should include an assessment of the area mentioned below;
  - Clinical site evaluation
    - Assess the volunteer (or patient) population pool
    - Evaluate CRO procedures for handling an unexpected and serious adverse event (AE) investigation.
    - Assess training records for the clinical team.
    - Evaluate CRO's ability to coordinate plasma/urine shipments to different bio analytical facilities
    - Assess ability to coordinate functional handoffs (e.g. Timely delivery of protocol to clinic, samples to lab, bio analytical data to the pharmacokineticist)
    - Assess clinical project management capabilities
  - Clinical data management
    - Assess the validation of the data collection system
    - Evaluate query generation, SOPS, CRF and database correction, change control
    - Evaluate clinical deliverables, CRFS (CRO or sponsor format) Data Base (when applicable)
    - Blood/plasma/urine collection procedures/SOPS and transport procedures to bio analytical unit.
    - Content of the written clinical report (i.e., CRO clinical report to be incorporated into the final study report)

- Bio analytical site qualification
  - Candidate CROs for bio analytical laboratory work (for drug, metabolite or biomarker assay) should also be assessed.
  - The company audit should also include cGLP compliance and an assessment of the laboratory's inspection history. Copies of the inspection history with all FDA 483s and EIRs should be reviewed.
  - Laboratory project manager should be assessed for their ability to coordinate all processes with client, clinic and pharmacokinetic.

- Pharmacokinetic site qualification
  - The pharmaceutical firm should also qualify the CRO site (or department) that is responsible for PK and statistical analyses and completion of the final integrated report.
  - During the pharmacokinetic site audit, following areas should be assessed:
    - Qualification of pharmacokinetic and statistical personnel.
    - Validation of pharmacokinetic and statistical programs (usually SAS).
    - Compliance with 21CFR(code of federal regulation) Part 11. At the time of this publication, full and complete compliance with Part 11 was not being enforced. However, the CRO should have a written plan and timeline for bringing all post laboratory functions into compliance.

Thank you