- An Abbreviated New Drug Application (ANDA) is specifically designed for an approval of a generic drug product.
- When data within an ANDA are submitted to the Food and Drug Administration's Center for Drug Evaluation and Research (CDER), office of Generic Drugs, the applications are reviewed and approved from that division.
- On approval of the application the applicant may manufacture and market the generic drug product with the purpose of providing consumers with a safe, effective, and low cost alternative of the generic form of a brand name drug.

- A generic drug must be a drug product that is comparable to an innovator drug product in dosage form, strength, route of administration,

quality, performance characteristic and intended use.

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term restoration Act of 1984, also known as the Waxman-Hatch Act. This act permits the FDA to approve ANDAs submitted to market generic versions of brand-name drugs without conducting costly and duplicative preclinical and clinical trials.

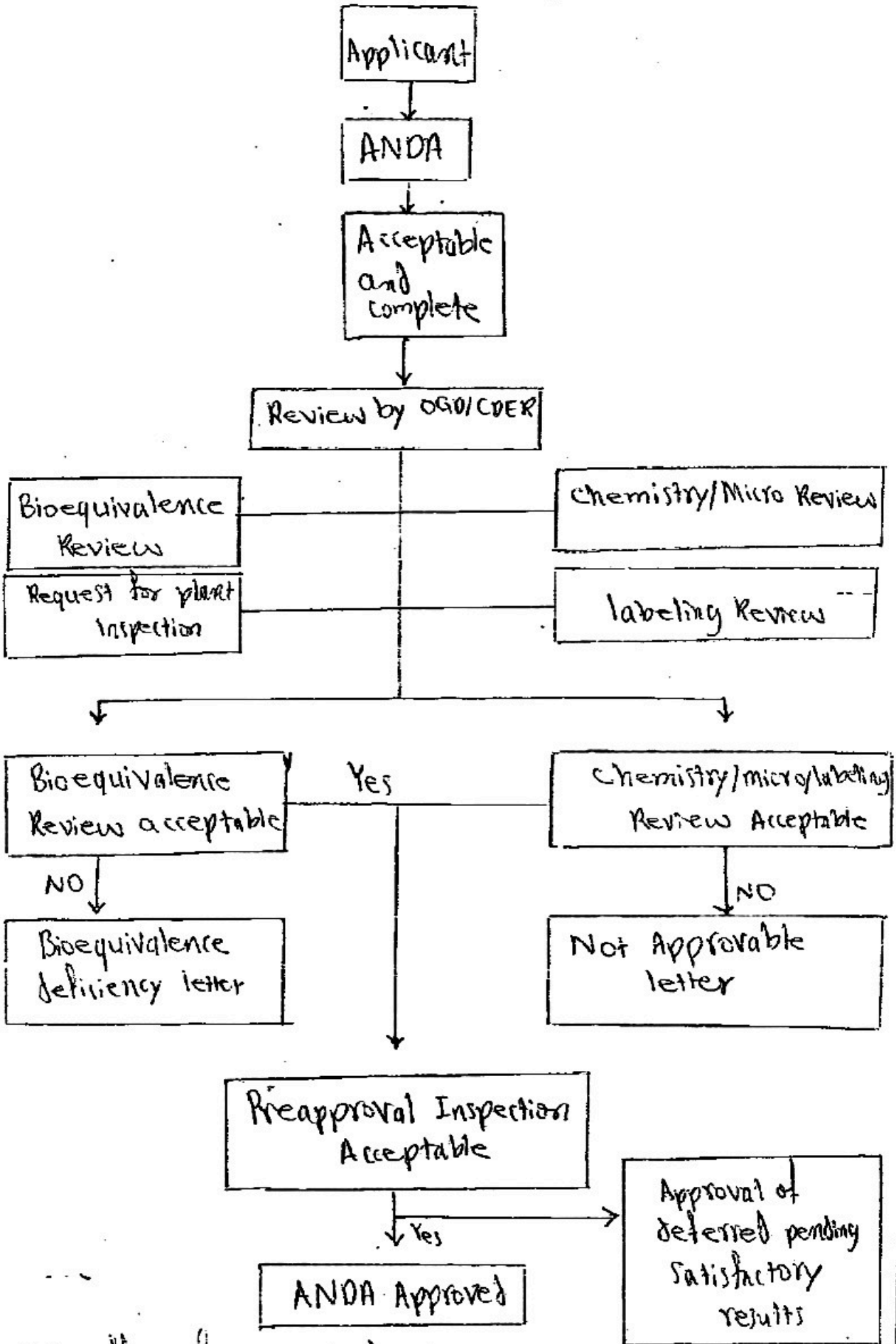
□ Hatch-Waxman Act:

- Commonly known as "Drug Price Competition and Patent Term Restoration Act" of 1984.
- The Hatch-Waxman Act" is an act dealing with the approval of generic drugs and associated conditions for getting their approval from

FDA, patent term extension and Orange Book listing.

- It is because of this Act that there is the availability of less costly generic drugs into the market without conducting costly and duplicative clinical trials.
- As the same time, the brand-name companies (innovators) can apply for upto five additional years longer patent protection for the new medicines that they developed to make up the time lost while their products were going through FDA's approval process.

ANDA review process



OGD: Office of generic drugs
CDER: Center for Drug Evaluation and Research

Guidance documents for ANDAs

- **Generics**
  - Generic (Draft - Distributed for comment purposes only)
  - Procedural Draft: Applications covered by Section 505(b)(2). This provision permits FDA to rely, for approval of an NDA, on data not developed by the applicant.

- **Biopharmaceutics**
  - Bioavailability and bioequivalence studies for orally administered drug products - general considerations. This guidance should be useful for applicants planning to conduct bioavailability (BA) and Bioequivalence (BE) studies; during the IND period for an NDA, BE studies intended for submission in an ANDA and BE studies conducted in the post approval period

for certain changes in both NDAs and ANDAs.

• Drug master files

• A Drug Master File (DMF) is a Submission to the 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.

• Required specifications for FDA's, IND, NDA and ANDA Drug Master File Binders.

• Guidance for industry

◦ changes to an approved NDA or ANDA

• Refusal to receive

◦ clarifies CDER's decisions to refuse to receive an incomplete application.

• Inactive ingredient database:

◦ This database contains all inactive ingredients

present in approved drug products or conditionally approved drug products currently marketed for human use.

oBiopharmaceutics

Bioavailability and Bioequivalence Studies for orally Administered Drug Products - General Considerations.

1. Introduction

2. Background

a. General

b. Bioavailability

c. Bioequivalence

3. Methods to document BA and BE

a. pharmacokinetic Studies

b. Pharmacodynamic Studies

4. Comparison of BA measures in BE studies

5. Documentation of BA and BE.

a. Solutions

b. Suspensions

c. Immediate-Release Products: Capsules and Tablets

d. Modified-Release Products

e. Miscellaneous Dosage Forms

6. Special Topics:

a. Food-Effect Studies

b. Moieties to be measured

c. Long-Half-life Drugs

d. First Point Cmax

e. Orally Administered Drugs Intended for Local Action

f. Narrow Therapeutic Range Drugs

I. ANDA content:

A. General:

- The term abbreviated is used in generic drug applications because they are generally not

required to include preclinical and clinical data to establish safety and efficacy.

- A sponsor of a generic drug must scientifically demonstrate that the product is bioequivalent i.e. performs in the same manner as the innovator drug.

- One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the blood stream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability of the generic drug, which they can then compare to that of the innovator drug. This 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.

B. Legal Requirements and Guidance Documents

- Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants or sponsors to provide guidelines for the processing, content, evaluation, and approval of an application and also to the design, production manufacturing and testing of regulated products.
- They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. It must be guidance documents are not regulations or laws and as a result are not enforceable either through administrative actions or through the courts.

The guidelines to assist in preparing ANDAs include:

1. Format and content for:

a. Application summary

b. chemistry, manufacturing and control section.

c. Nonclinical pharmacology and toxicology section.

d. Human pharmacokinetics and bioavailability section.

e. clinical and statistical section

f. Microbiology section.

2. Guideline for post marketing reporting of adverse reactions.

3. Guideline for the submission in microfiche of the archival copy of an application.

4. Guideline for submitting supporting documentation for the manufacture of drug substance.

5. Guideline for submitting supporting docu-

mentation for the manufacture of finished dosage-forms.

6. Guideline for submitting supportive analytical data for methods validation in new drug applications.

7. Guideline for submitting supporting documentation for stability studies of human beings and biologics.

8. Guideline for packaging.

II. ANDA check list:

The ANDA check list provides the applicant with an itemization of all the necessary components for an ANDA submission.

III. Additional comments Regarding the ANDA:

Each component and section of the checklist

should be carefully reviewed for content and completeness. Every precaution must be taken so that the applicant does not receive a letter of Refusal to Receive that clarifies the CDER's decision to refuse to receive an incomplete application. The specific copies i.e, archival, review, and field to be submitted in the ANDA, outlined in the beginning of the checklist, should follow the NDA format as stated below:

a. Archival copy:

- Cover letter
- Application form
- ANDA Suitability Statement
- Chemistry, manufacturing and controls
- Human pharmacokinetics and bioavailability
- Samples and labeling section
- Other information

b. Review copy:

Each of the technical sections in the review copy of the ANDA must be separately bound in its own particular color folder, and a copy of the application form must also be included. Although an integrated summary is not required, a summary that would help in reviewing chemist may expedite the ANDA approval.

C. Field copy:

A field copy certification with an original signature of the chemistry, manufacturing and control with a copy of application form and any reference to Drug Master Files should be clearly explained.

Summary:

ANDAs are specifically designed to help

the manufacturers of generics to provide these products rapidly to the consumer at lower cost than those of brand names.

ANDA (Abbreviated new drug application)

- ANDA is an application for a U.S. generic drug approval for an existing licenced medication or approved drug.
- ANDA is submitted to FDA's center for drug evaluation and Research office of generic drugs (OGD), which provides review and ultimate approval of generic drug product.
- Once approved, an applicant may manufacture and market the generic drug product to ... provide safe, effective and low cost alternative to the American public.
- Generic drug product is one that is comparable to an innovator drug product in
  - dosage form
  - Strength
  - route of administration
  - quality
  - Performance characteristics
  - intended use
- All approved products, both innovator and

generic are listed in FDA's approved drug products ē therapeutic equivalence eval.. (orange book).

- Generic drug applications are termed as abbreviated because they are generally not required to include preclinical (animal and in vitro) and clinical (human) trial data to establish safety and effectiveness.
- Scientific demonstration of bioequivalence-- is important and must insted, generic applicant must scientifically demonstrate that their product is bioequivalent (performs in same manner as innovator drug)
- One way scientistis demonstrate bioequivalence is to measue time it takes the generic drug to reach the blood stream in 24-36 healthy volunteers.
- This gives them the rate of absorption or bioavailability of generic drug, which they can them compare to that of the innovator drug.

Necessary items of ANDA:

- → Composition of drug:
  - → name
  - → Amount of each ingredient < active / inactive

- Identify place of drug { manufactured / Processed / Packaged / labeled }
  - name of supplier
- Identify any person other than applicant who performs a part of operation
- Certifications from applicant and
  - method used in { Process / facilites / Controls → use in { mfg / processing / packaging / labeling }
- Assure that dosage form and comply ~ specifications and tests ~ official compendi
  - component

- if drug differ from compendium drug, the specification and tests applied to drug and its components are adequate to assure their identify, strength, quality, quantity.

- Outline { method used
  facility
  control used for ← mfg, Processing, packaging

- if drug require a long ANDA
  require adequate data to assure bioavailability

□ Goals of ANDA:

↓ price of drug
↓ time of development
↑ bioavailability of drug (compare to reference list drug)

□ WAXMAN-HATCH ACT:

-Using the bioequivalence as the basis for approving generic copies of products was

established by drug price and patent term restoration act" of 1984 is known as Waxman-hatch act.

- This act expedites the "availability" of less costly generic drugs by permitting FDA to approve application to market generic versions of brand names without conducting costly clinical trials.

- Also it provides mechanism to grant drug companies upto 5years additional parent -- protection to compensate patent life lost as a result of time consumed during test required by FDA.

- Condition to ask an extension:

- Patent must not have expired at time of filling the request for extension.

- Product must have been subjected to examination by FDA.

- Request for extension must have been filled

at least during the last three months of life of patent.

- A fee of 750 $ is paid.

#ANDA requirements:

1- labeling
2- Pharm/tox
3- Chemistry
   Manufacturing
   controls
4- Microbiology
5- Inspection
6- Testing
7- bioequivalence

1- Labeling:

- Same information as brand name labeling
- May differ in excipients and description (color - shapes).

2- Pharm/tox:

- All inactive ingredients must be approved in either reference list or similar NDA in same or higher levels.

3. Chemistry, manufacturing and controls:

- Component and composition
- Mfg and controls
- Batch formulation and records
- Description of facilities
- Packaging
- Stability

4. Microbiology:

- for antiinfective drug
- A complete description of biochemical basis of drug action on microbial physiology.
- Clinical microbiology laboratory methods
- Assure the sterility of products especially ē injectables.

□ Inspection / testing:

- Assure mfg facilites are incompliance ē current GMP's.
- Assure bioequivalence. sites are in compliance ē GCP's.

□ Bioequivalence:

A generic drug is considered to be bioequivalent to brand name if rate and extent of absorption not show a significant difference from listed drug.