ANDA - Abbreviated New Drug Application

NDA vs. ANDA Review Process

S.No.	Brand Name Drug NDA Requirements	S.No.	Generic Drug ANDA Requirements
1	Chemistry	1	Chemistry
2	Manufacturing	2	Manufacturing
3	Controls	3	Controls
4	Labeling	4	Labeling
5	Testing	5	Testing
6	Animal Studies	6	Bioequivalence
7	Clinical Studies		
8	Bioavailability		

- ANDA is an application for a U.S. generic drug approval (for an existing licensed approved drug).
- The ANDA is submitted to office of Generic drugs US.
- After review of the documents USFDA gives approval as generic drugs.
- After approval, an applicant may manufacture and market the generic drug product to US market.
- A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, and route of administration, quality, performance characteristics and intended use.

- All approved products, both innovator and generic, are listed in FDA's 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 .
- Generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug) by doing bioavailability study.

- The generic drugs must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.
- Bioequivalence studies are critical component of ANDA submissions.
- The purpose of these studies is to demonstrate equivalence between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug.
- Together with the determination of pharmaceutical equivalence, establishing equivalence allows a regulatory conclusion of therapeutic equivalence.
- India is having highest no. of USFDA approved manufacturing sites in world.

Biological classification of drugs

Based on drugs solubility and permeability following is the biopharmaceutical classification.

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

- BCS classification is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability .

- This is a formulation development tool.

- The classification can be used as a basis for setting in vitro dissolution specifications and also as a basis for predicting successful in vitro –in vivo co relation(IVIVC).

General assumptions based on Biopharmaceutical system:

- Class I drug products are mostly bioequivalent .
- Class II drugs are usually bioequivalent if dissolution profile matches in pH 1.0, 4.5, 6.8 .
- Class III drugs are bioequivalent if study is powered account for variability.
- Class IV drugs are often unpredictable.

Examples :

Class I drug	Class II drug	Class III drug	Class IV drug
Metoprolol HCl	Mefenamic acid	Cimetidine	Hydrochlorothiazide
Diltiazem HCl	Nifedipine	Acyclovir	Furosemide
Verapamil HCl	Glibenclamide	Captopril	

- **Solubility :**

  Drug substance is considered as highly soluble when highest dose strength is soluble in 250 ml or less of aqueous media over pH range of 1.0 -7.5 .

- **Permeability:**

  The permeability class boundary is based on the extent of absorption of drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane.

Patent certification options:

- Paragraph I = Required patent information has not been filled.
- Paragraph II = Patent has expired.
- Paragraph III = Patent has not expired but will expire on a particular date .
- Paragraph IV = Patent is invalid or non infringed by generic applicant.

Stages in formulation development

S. No.	Activity
1	Literature / Patent search and clearance /Market search .
2	Innovator samples availability / characterisation and multimedia dissolution /Test license application with FDA .
3	DMF grade API availability and request for working standard / impurity standards / tooling such as punches .
4	Analytical method development & finalisation of API Specifications like particle size. Method development for assay , related substances , dissolution .
5	Formulation development / Stability study /IIG clearance /USP grade excipients / Preformulation studies .
6	Multimedia Dissolution studies and comparison with innovator sample f2 value . Dissolution at different RPM .
7	Pilot bio study / Stability study /Packing material finalization

8	Analytical method validation .
9	Formulation development report .
10	Hardness and other ruggedness trials .
11	Master formula card preparation .
12	Scale up and exhibit batch at USFDA approved site .
13	Multimedia dissolution and comparison F2 Value.
14	Pivotal BE .
15	Stability study as per ICH .
16	Filing .
17	Approval.
18	Commercialisation .

Literature / Patent search and clearance /Market search

- Before finalizing a formulation, market research is must for knowing potential of the molecule in US market and subsequent value addition to business.

- Product patent clearance is required for proceeding ahead towards formulation development.

Innovator samples availability / characterisation and multimedia dissolution / Test license application with FDA

- For procuring RLD (Reference listed drug) from US one has to take import permission from DCGI , followed by custom clearance is needed.
- Reference listed drugs are listed in orange book .
- Need to make application with local FDA for test and trial application for initiating development .
- After receipt of innovator samples it is required to carry complete physical and chemical characterization of innovator samples.

Physical characterization includes:

Description

Tablet dimensions

Hardness

Disintegration time.

Chemical characterization includes :

Analytical method development for dissolution

Related substances

Organic volatile impurities

Assay

Multimedia dissolution .

API Availability

- For US market it is compulsory that the API manufacturer is having DMF for API.
- We should get patent clearance from IPM before finalization.
- We need to finalize additional in house specifications such as particle size.
- It is also mandatory that excipients used in the formulation should comply as per USP.
- Organize suitable tooling such as punches for development.

Analytical method development

- It is required to organize working standards, impurity standards form vendor or from authorized source.
- Also need to organize reagents , HPLC columns for carrying analysis.
- Need to carry out complete characterization of innovator samples as this is basis against which we will be comparing all future analytical data.
- Required to finalize method for particle size determination.

Formulation Development

- We need to send formulation tentative strategies to IPM before initiating development.
- Carry out short term preformulation studies.
- Plan trials & optimize formulation .
- Develop formulation closer to innovator sample.
- Plan multimedia dissolution. Ensure that F2 value (similarity factor) across all dissolution media is more than 50 .

  As F2 value more than 50 ensures sameness or equivalence.

- Confirm all excipients used are in the limit as per IIG.

- IIG is a data base which gives maximum daily acceptable intake of particular excipient .

- Carry out all ruggedness trials viz :
  - Effect of hardness,
  - Effect of moisture,
  - Effect of kneading,
  - Effect of blending, etc.

Exhibit batches

- After successful completion of short term stability at R & D level and successful pilot bio studies , product is planned at production site.
- Site where we intend to manufacture product should be USFDA approved.
- Formulation development report is prepared based on various trials taken during development and related analytical data.
- Analytical method validation is performed.

- Manufacturing license is taken at production site.
- Formulation Scientist issues bill of material to purchase department to procure API , excipients and packing material.
- Master formula card and analytical master documents are send to plant for review , organizing tooling, checking environmental conditions, availability of equipments .
- Based on master formula card batch manufacturing record is prepared .

- After receipt of RM/ PM needed for batch , a complete analysis is being done.

- After release of materials exhibit batch is planned at production level.

- As per USFDA guidelines batch size should be such that final desired packed quantity should be minimum 1.0 lac units.

- After successful completion of exhibit batch complete analysis is done.

- Multimedia dissolution against innovator samples is carried out.
- Samples are kept for stability in final pack as per ICH guidelines.
- Pivotal biostudy is planned.

Bio studies

Bioavailability :

It is defined as the rate and extent to which active ingredients or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalence :

The absence of a significant difference in the rate and extent to which the active ingredients becomes available at the site of action when administered at the same mole dose under similar conditions.

For BE study two formulations should have :

- Same active ingredients
- Same route of administration
- Same dosage form
- Same strength
- Same indications

- To measure bioavailability and to establish bioequivalence of a product is important for ANDA submission.
- BA data provides an estimate of the fraction of drug absorbed, as well as subsequent distribution and elimination.
- For two orally administered drug products to be bioequivalent, the active ingredient in the test must exhibit the same rate and extent of absorption as the reference drug product.
- The true dose is not the drug present in the formulation but is the drug available in the body to exert its effect.

Drug available in body will depend on

DISSOLUTION -- ABSORPTION – METABOLISM

Rate of absorption is reflected by T_{max}

Extent of drug absorption is reflected by AUC.

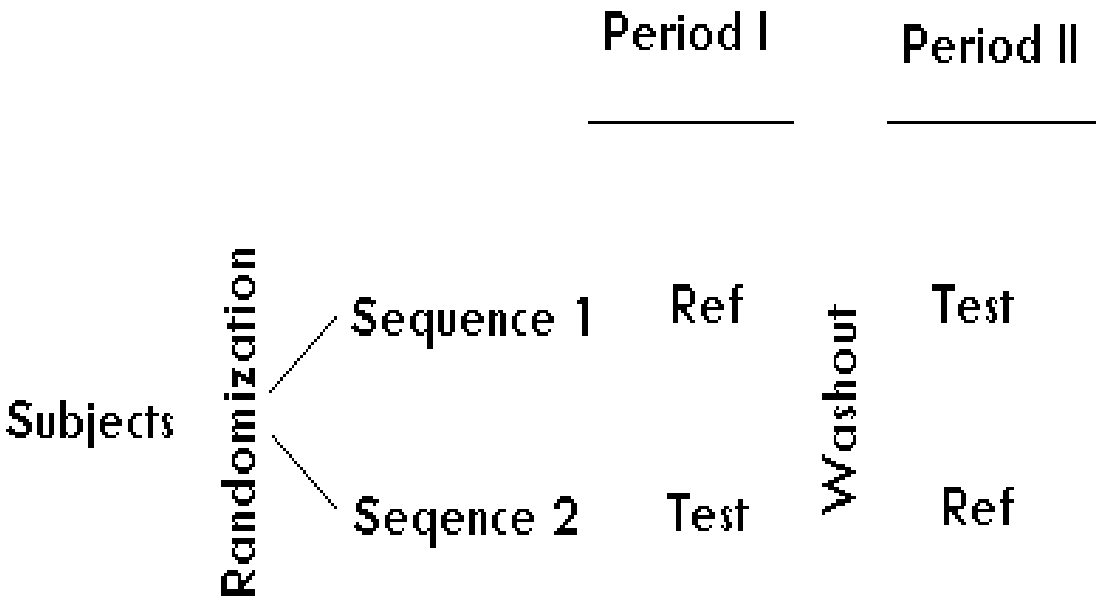
Both rate and extent of absorption affect C_{max}

- Bio studies are required for ANDA submission.
- Before pivotal bio studies pilot studies are conducted.
- Pilot biostudy is conducted on lesser no of patients for increasing success in pivotal bio study.
- Pilot bio study is also used to validate analytical methodology , optimize sample collection time intervals and provides other information .

- The bio study is generally conducted standard 2 x2 cross over fashion. This study is designed to avoid variability and is globally acceptable and widely used design .

- Duration of washout period for cross over design should be approximately > than 5 times the plasma terminal half life.

Study design
standard 2 x 2 crossover



- Subjects recruited for in vivo studies should be 18 years of age or older.
- The bioanalytical method should be accurate , precise, selective , sensitive and reproducible.
- C max and AUC are the parameters considered for product quality for BA and BE studies.
- Minimum no. of patients to be evaluated should be at least 12 nos.
- Fasted and fed study is recommended for extended release formulation for knowing food effect.

- The CDER recommends statistical analysis. This involves calculation of 90 % confidence interval for the ratio of average of test & reference.
- For area under curve (AUC)and Peak concentration (C max) the limit is 80 - 125 % for the ratio of product averages.
- The dissolution should be conducted in general on 12 tablets .
- The methods used for dissolution are :

Basket method apparatus : RPM 50-100

Paddle method apparatus : RPM 50 -75

Volume : 500 /900 /1000 ml.

Steps

- Filling review
- Coordination of generic drug review process
- Bioequivalence review process
- Chemistry review process
- Labeling review process
- Putting it all together

Filling review

- The process begins when an applicant submits an ANDA to the OGD.
- The document room staff assigns it an ANDA number and stamps a received date on the cover letter of ANDA.
- It is sent to a consumer safety technician who reviews the preliminary sections of ANDA checklist.
- With in first 60 days – submission, filling review is completed. Regulatory support branch (RSB) is responsible for this process.

Filling review

- The patent certification and exclusivity statement must address all existing patents and exclusivities for the RLD (Reference List of Drugs) published in the "Approved Drug Products with Therapeutic Equivalence Evaluations" commonly known as ORANGE BOOK.
- If an RLD has expired patents ,an applicant may certify that no relevant patents remain.
- The review of patents and exclusivities is an ongoing process throughout the review cycle, as new patents and exclusivities may become listed in the orange book.

Filling review

- Once the RSB (Regulatory support branch) completes the filling review of the ANDA and verifies that the application contains all the necessary regulatory requirements an “Acknowledgement” letter is issued to the applicant indicating its acceptance for filling and the official filling date.
- The application is then assigned to technical reviewers.
- If the ANDA does not met the criteria for filling ,
- a “ refuse –to-receive “ letter is issued with a list of deficiencies.

Filling review

- Upon filling an ANDA, the RPM (RSB Project manager) forwards an establishment evaluation request (EER) to the office of compliance.
- Office of Compliance are operating in compliance with current Good Manufacturing Practice (cGMP) regulations.
- Currently ANDA can be submitted entirely electronically.

Coordination of the Generic Drug Review Process

- Now application enters the review queue, This means that the application is assigned to a bioequivalence reviewer, a chemist and a labeling reviewer.
- Each chemistry team consists of a team leader, a project manager and several reviewers .
- The chemistry project manager serves as the “Applicant” project manager (APM), they plan, organize and coordinate all of the review activities for the applications that they manage.

Bioequivalence Review Process

- The BE section is assigned to the division of bioequivalence to review.
- Bioequivalence project manager (BPM) access list of pending ANDA assign to individual reviewers according to “first-in, first-reviewed” policy.
- The DBE’s responsibilities include BE section of ANDA, Bio-investigational new drug applications (Bio-INDs), protocols and controlled correspondence.

Bioequivalence Review Process

- The BPMs request and track inspections of the clinical and analytical sited through the division of scientific investigations (DSI).
- If BE reviewer requires information to complete the review-- First consult the team leader and then the BPM to obtain information from applicant.
- If issue is resolved with in 10 working days, teleconference is initiated by BPM.
- The applicant response to the teleconference is labeled as “Bioequivalence Telephone Amendment”

FDA requires an ANDA applicant to provide information to establish bioequivalency.

It includes:-

- A formulation comparison for products whose bioavailability is self evident. e.g., oral solutions, injectables, ophthalmic solutions where the formulations are identical.
- Comparative dissolution testing where there is a known correlation between in vitro & in vivo effects.
- In vivo bioequivalence testing comparing the rate & extent of absorption of the generic to the reference product
- For non classically absorbed products, a head to head evaluation of comparative effectiveness based upon clinical end points

Chemistry Review Process

- The chemistry ,manufacturing and controls (CMC) section of the application is assigned to the app chemistry division and team based on therapeutic category of the drug product.
- The team leader assigns the application to a reviewer on his/her team according to the “first-in, first reviewed policy”.
- The Chemistry division reviews CMC section Of ANDA, drug master files , annual reports and controlled correspondence.

Chemistry Review Process

- They are organized in to review teams consisting of six reviewers and a team leader.
- Team leaders perform secondary review.
- Tertiary review is by deputy director rather than by division director in BE review.
- The goal of the chemistry review process is to assure that the generic drug will be manufactured in a reproducible manner under controlled substances

Labelling Review Process

- Labeling section of the application is assigned to the app labeling reviewer based on the therapeutic category of the drug product.
- The labeling review branch is part of DLPS.
- A team leader oversees the work of 4-6 reviewers.
- The basis for the labeling review is to ensure that the generic drug labeling is the “same as” the RLD labeling.

Labelling Review Process

- The labeling reviewer identifies and resolves concerns about medication errors. Ex: sound alike or legibility of drug names on a container label.
- To ensure that the proposed labeling in an ANDA is the “same as” the RLD,
- The reviewer must first identify the RLD
- Next step is to find the most recently approved labeling for the RLD.
- If it is not the recently approves, it is considered as discontinued labeling (so not acceptable for labeling review).

Labelling Review Process

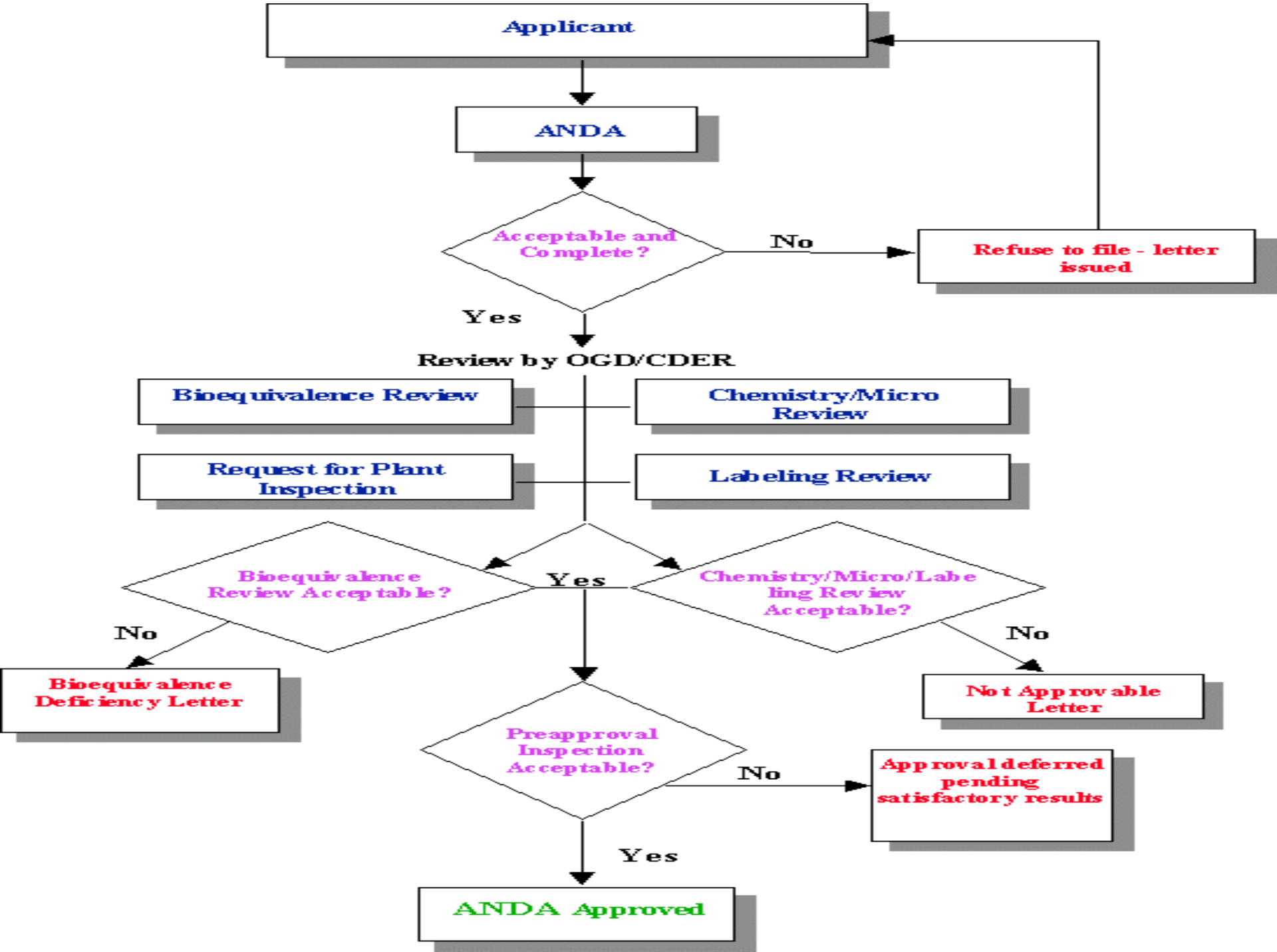
- The applicant may submit four copies of draft labeling or 12 copies of final printed labeling as proposed labeling. They are submitted for tentative approval.
- The labeling branch supports the submission of electronic labeling which is preferred and strongly encouraged.
- As the container label is reviewed, the labeling reviewer decides of the labeling is easy to read and positioned in accordance with the regulations.

Putting It All Together

- After the final office level administrative review and individual disciplines have resolved their deficiencies, the application will either receive a full approval or a tentative letter.
- When the review of an ANDA is completed, the APMs draft the app approval letter and circulate it with the reviews and application for concurrence.
- The APMs communicate with the OGD management on a weekly basis to update them on the progress of reviews.

Putting It All Together

- A full approval letter details the conditions of approval and allows the applicant to market the generic drug product.
- A tentative approval letter is issued if there are unexpired patents or exclusivities accorded to the RLD, and delays the marketing of the product .
- Once the office director has signed the final approval letter, APM calls and faxes a copy of the approval letter to the applicant.
- The document room staff then mails the final approval letter to the applicant.


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
Bioequivalence Deficiency Letter
No
Not Approvable Letter
Preapproval Inspection Acceptable?
No
Approval deferred pending satisfactory results
Yes
ANDA Approved

- For More Information:

1. FDA Guidences for Industry
   (http://www.fda.gov/cder/guidence/index.htm)

2. FDA- Division Office of Generic Drugs
   (http://www.fda.gov/cder/ogd/)

3. United States Pharmacopiea
   (http://www.usp.org)

THANK YOU

Concept of Generics

Introduction

- A generic drug is a medication that has exactly the same active ingredient as the brand name drug and yields the same therapeutic effect. It is the same in dosing, safety, strength, quality, the way it works, the way it is taken, and the way it should be used.
- Generic drugs do not need to contain the same inactive ingredients as the brand name product.
- However, a generic drug can only be marketed after the brand name drug's patent has expired, which may take up to 20 years after the patent holder’s drug is first filed with the U.S. Food and Drug Administration (FDA).

- Generic drugs are usually much less expensive than brand name drugs once they reach the market.
- A drug company develops new drugs as brand name drugs under patent protection. This protects their investment in drug research by giving the drug company the sole right to manufacture and sell the brand name drug while the patent is in effect.
- When patents or other periods of exclusivity expire, other manufacturers can submit an abbreviated new drug application (ANDA) to the FDA for approval to market a generic version of the brand name drug.

Are generic drugs as safe as brand name drugs?

- Yes.
- The FDA must first approve all generic drugs before they are marketed.
- The FDA requires that generic drugs must be as high in quality, and as strong, pure and stable as brand name drugs.
- Generic drugs use the same active ingredients as brand name drugs and work the same way.
- They have the same risks and the same benefits as the brand name drugs.

Why are generic drugs cheaper?

- Although generic drug active ingredients are chemically identical to their branded counterparts, they are typically sold at a cheaper price than the brand name drug.
- Generics are less expensive because the drug manufacturer does not have to duplicate the original clinical trials for effectiveness and safety, which lowers the cost to bring the drug to market.
- Generics are not less expensive because they are lower in quality.

Are generic drugs always cheaper?

- Usually.
- However, when a generic drug is first approved and marketed, costs may remain high (although less than the brand name drug) for 6 months because the FDA will give the first generic manufacturer a “180-day exclusivity period”.
- The “180-day exclusivity” is assigned to the generic manufacturer who is the first to file an ANDA and has done the additional work to get the generic drug to market.
- This exclusivity allows the company to be the first -- and possibly only -- generic on the market for 6 months.

- Generic manufacturers may charge higher prices during this time because there is little to no other generic competition.
- Generic companies state that exclusivity allows them to recoup expenses related to being the first to bring a generic to market.
- Quite often this is a disadvantage to the consumer, who gets stuck with the higher priced generic for 6 months.
- If more than one generic manufacturer files their ANDA at the FDA on the same day, these companies would share the 180-day exclusivity, which might lead to somewhat lower prices during the 180-day period due to competition, but possibly not as low as when several generics enter the market.

What standards must generic medicines meet to receive FDA approval?

- Drug companies must submit an abbreviated new drug application (ANDA) to FDA for approval to market a generic drug that is the same as (or bioequivalent to) the brand product.
- FDA reviews the application to ensure drug companies have demonstrated that the generic medicine can be substituted for the brand-name medicine that it copies
- An ANDA must show the generic medicine is equivalent to the brand in the following ways:

- The active ingredient is the same as that of the brand-name drug/innovator drug.
  - An active ingredient in a medicine is the component that makes it pharmaceutically active — effective against the illness or condition it is treating.
  - Generic drug companies must provide scientific evidence that shows that their active ingredient is the same as that of the brand-name medicine they copy, and FDA must review that evidence.
- The generic medicine is the same strength.
- The medicine is the same type of product (such as a tablet or an injectable).
- The medicine has the same route of administration (such as oral or topical).
- It has the same use indications.

- The inactive ingredients of the medicine are acceptable.
  - Some differences, which must be shown to have no effect on how the medicine functions, are allowed between the generic and the brand-name product.
  - Generic drug companies must submit evidence that all the ingredients used in their products are acceptable, and FDA must review that evidence.
- It lasts for at least the same amount of time.
  - Most medicines break down, or deteriorate, over time.
  - Generic drug companies must do months-long "stability tests" to show that their products last for at least the same amount of time as the brand-name product.

- It is manufactured under the same strict standards as the brand-name medicine.
  - It meets the same batch requirements for identity, strength, purity, and quality.
  - The manufacturer is capable of making the medicine correctly and consistently.
    - Generic drug manufacturers must explain how they intend to manufacture the medicine and must provide evidence that each step of the manufacturing process will produce the same result each time. FDA scientists review those procedures, and FDA inspectors go to the generic drug manufacturer's facility to verify that the manufacturer is capable of making the medicine consistently and to check that the information the manufacturer has submitted to FDA is accurate.
    - Often, different companies are involved (such as one company manufacturing the active ingredient and another company manufacturing the finished medicine). Generic drug manufacturers must produce batches of the medicines they want to market and provide information about the manufacturing of those batches for FDA to review.

- The container in which the medicine will be shipped and sold is appropriate.
- The label is the same as the brand-name medicine's label.

- The ANDA process does not, however, require the drug applicant to repeat costly animal and clinical (human studies) on ingredients or dosage forms already approved for safety and effectiveness. This allows generic medicines to be brought to market more quickly and at lower cost, allowing for increased access to medications by the public.