

ANDA- Abbreviated New Drug Application

Definition of a Generic Drug

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

Basic Generic Drug Requirements

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

- An “**Abbreviated New Drug Application**” (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug.
 - *termed as "abbreviated" because they generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.*
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Hatch-Waxman Act:

- Hatch-Waxman Act, proposed by Senators Orrin Hatch and Henry A. Waxman was approved in 1984, making it easier for generic drugs to enter the market.
 - Generic drugs always been available in US market.
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- In fact, the US Food and Drug Administration (FDA) approved many generic drugs before 1984, using three separate approval mechanisms:

the Abbreviated New Drug Application (ANDA) for drugs originally approved before 1962;

the “paper NDA,” a type of New Drug Application (NDA) for generic copies of drugs approved after 1962;

and the monograph system for generic antibiotics and insulin.

ANDA

- Before 1962, NDAs had been approved solely on the basis of data demonstrating that the drug was safe, as there were no efficacy requirements.
- Beginning in 1968, drugs that had been approved between 1938 and 1962 only on the basis of safety were gradually evaluated by FDA's Drug Efficacy Study Implementation (DESI)
- program for evidence of efficacy by evaluating the drug's marketing history, published clinical studies and the views of outside experts.
- In a sense, the existence of the DESI program enabled FDA to approve ANDAs.
- FDA began approving ANDAs in 1968 for generic copies of drugs that had originally been approved between 1938 and 1962.
- ANDAs were approved if the generic was bioequivalent to the original product (although bioequivalence studies were not always required) and if the original had been found effective by the DESI program.

- **DESI:** Drug Efficacy Study Implementation.
 - When the DESI program was in progress, the agency estimated that there were between 5-13 products without NDA's that were identical and similar to each of the 13,000 products that held NDA's under the 1938 Act.
 - These products contain same active ingredients in the same amount and dosage form, often though they claim some unique characteristics i.e., a different salt or ester, a different amount, a different dosage form or an extra added ingredients.
 - As part of the DESI project the FDA thought to introduce uniformity and control over these products.
 - First, the agency said that a copy had to be identical, unless the proponent got FDA permission to vary from the innovator.
 - Second, the manufacturer had to obtain an ANDA showing that the product was identical.
 - In essence, it was an application that contain all the CMC of a full NDA, but omitted any preclinical or clinical data. A number of generic firms opposed even these requirements and significant litigation followed.
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- Physicians were reporting that CHF patients who had been treated carefully with a specific dose of Digoxin, went out of control upon getting prescriptions refilled.
 - Investigations revealed that Digoxin, a pre 1938 drug that never subject to an NDA, varied from manufacturer to manufacturer not in quantity of actual drug per tablet, but in the amount of drug released from the tablet into the body.
 - The consequences could be life threatening.
 - The agency responded with an order that each manufacturer submit an ANDA that included bioavailability studies showing the rate and extent of absorption into the body.
 - Thus, was born an idea of bioequivalence: that competing products not only be pharmaceutically identical but also show no significant difference in the rate and extent of absorption in controlled bioavailability studies.
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- The ANDA process and bioequivalence permitted the agency for the first time to declare individual generic products to be therapeutically equivalent to approved brand drug.
 - The FDA began making such declarations in 1975, 1976 and 1979, the agency began to publish them in orange book.
 - The generics doesn't have a great competitive threat because state pharmacy laws did not permit the substitution of a generic drug for the innovator drug.
 - In 1979 the federal trade commission revealed a model state drug product selection law, which guided state legislatures how to amend pharmacy laws to permit druggists to substitute equivalent generics for innovators without the permission of the prescribing physicians.
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Paper NDAs :

- In 1978, FDA expanded the generic approval program with the paper NDA mechanism
- approving generic copies of drugs that had been approved as new drugs after 1962 (i.e., drugs that had not been subject to the DESI review)
- based upon published studies to support safety and efficacy that the generic applicant submitted in an NDA.
- Bioequivalence studies were required in some cases.
- Nineteen original products served as reference drugs for 47 paper NDAs approved by FDA between January 1979 and June 1983.
- Additional paper NDAs were approved by FDA's Division of Anti-Infective Drug Products August 1983

Monographs for Antibiotics and Insulin

- Generic copies of antibiotics and insulin were approved under a monograph system from 1945 to 1997.
- The generic copy was required to:
 - meet originator product specifications as published in an FDA monograph
 - be shown to be bioequivalent to the originator product
 - undergo batch release testing by FDA (until batch release testing was fully eliminated in 1982)
- For antibiotics, the original marketing application was called a “Form 5” and the generic drug application was called a “Form 6.”

Hatch-Waxman Act

- Before the Hatch-Waxman Act was approved, only about 35% of brand name drugs had to content with a generic competitor; nowadays nearly all drugs are faced with generic copycats.
- The Hatch-Waxman bill (known officially as the Drug Price Competition and Patent Term Restoration Act) brought the following changes:
 1. Generic drugs no longer needed to prove their safety and efficacy. Under the bill, generic drug manufacturers need only submit an Abbreviated New Drug Application (ANDA) to prove their product's bioequivalence to the original branded drug. This is a cheaper process for manufacturers.
 2. Generic drugs are granted a 180-day period of exclusivity. Either the first drug to file an ANDA, or the first group of drugs, is granted this period.

3. Manufacturers filing ANDAs can only do so for drugs that have not been patented.

4. ANDAs can only be filed when a branded drug's patent has expired.

5. Generic drugs cannot go on to the market until the branded patent has expired.

6. Branded drug patents must not have been infringed or proven invalid. (If a patent is shown to be invalid, the FDA must wait 30 months until it approves a generic.)

7. Because branded drugs lose so much of their revenue when generic drugs are introduced, the Act provides them with patent extensions options, which now average about three years.

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- Under Hatch-Waxman, generic manufacturers may now seek FDA approval to market the
 - generic drug before the expiration of the patent of the branded product, via the Abbreviated New Drug Application (ANDA) Process
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Abbreviated New Drug Application (ANDA): Generics

- An ANDA contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product.
- Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.
- A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics.
- Generic applicants must scientifically demonstrate that their product is bioequivalent.
- One way to demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36hrs healthy, volunteers.
- This gives the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug.

Goal of ANDA:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.
- To reduce the price of the drug.
- To reduce the time development.
- Increase the bioavailability of the drug in comparison to references list drug.

Abbreviated or Supplemental NDA:

- Abbreviated NDA: includes..
 - Generic drug
 - New combination of approved drugs
 - Proportion of ingredients in combination is changed
 - Supplemental NDA: includes..
 - New intended use of the drug (labeling change)
 - Dose, method or duration of administration is changed
 - Change in manufacturing process or location
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Format of ANDA :

- Three copies of application are required,
 - an archival copy,
 - a review copy
 - and a field copy
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ARCHIVAL COPY

- The Archival Copy Contains all sections of the NDA, including the cover letter, Form FDA-356h (Application to Market a New Drug, Biologic, or an Antibiotic for Human Use), the administrative sections, Comprehensive NDA index, and All technical sections.
- It must contain four copies of the Labeling section.
- It must contain three additional copies of the CMC and Methods Validation Package in a separate binder.
- The archival copy is the only copy that contains the Case Report Tabulation and Case Report Forms.

REVIEW COPY

- The Review Copy Intended for reviewers in the corresponding technical disciplines.
 - In addition to the appropriate technical section, each review copy also includes The cover letter, Form FDA-356h, The administrative sections, Comprehensive NDA index Individual table of contents, The Labeling section, and The Application Summary.
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FIELD COPY

- The Field Copy required since 1993 for use by FDA inspectors during pre approval facilities inspections.
 - It includes the Cover letter and Form FDA-356h, the administrative sections, the comprehensive NDA index Individual table of contents, The Labeling section, The Application Summary, and CMC and Methods Validation Package
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- ANDA includes the following:

- Application form
 - Table of contents
 - Basis for ANDA submission
 - Conditions of use
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ANDA contents

- Section 1: Overall ANDA index
 - Section 2: Labeling
 - Section 3: Application summary
 - Section 4: Chemistry, manufacturing and controls
 - Section 5: Nonclinical pharmacology and toxicology
 - Section 6: Human Pharmacokinetics and bioavailability
 - Section 7: Microbiology
 - Section 8: Safety data
 - Section 9: Statistical data
 - Section 10: Case report tabulation
 - Section 11: Case report forms
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Overall ANDA index

- The NDA index is a comprehensive table of contents that enables the reviewers to find specific information in this massive document quickly.

Labeling:

- include all draft labeling that is intended for use on the product container, cartons or packages, including the proposed package insert
- “Same” information as brand name labeling
- May delete portions of labeling protected by patent or exclusivity (i.e., an indication, strength)
- May differ in excipients and product description (i.e., colors, shapes)

Application summary

- Pharmacology class, scientific rational, intended use, and potential clinical benefits
 - Foreign marketing history
 - Chemistry, Manufacturing and control summary
 - Nonclinical pharmacology and toxicology summary
 - Human pharmacokinetics and bioavailability summary
 - Microbiology summary
 - Clinical data summary and results of statistical analysis
 - Discussion of benefit/risk relationship
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Chemistry, Manufacturing and Controls (CMC):

- Components and composition
 - Manufacturing and Controls
 - Batch formulation and records
 - Description of facilities
 - Specifications and testing
 - Packaging
 - Stability
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Nonclinical pharmacology and toxicology

- Provide individual study reports, including pharmacology, toxicology, ADME studies.
 - Effects related to the therapeutic indication, such as the pharmacodynamic ED50 in dose- ranging studies and the mechanism of action (if known)
 - Interactions with other drugs (or cross-reference the location of the information in any of the above subsection
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Human Pharmacokinetics and bioavailability

- data from Phase I safety and tolerance studies in healthy volunteers
 - Summary of analytical method used in in-vivo biopharmaceutic study
 - Pilot or background studies
 - Bioavailability or bioequivalence studies
 - Pharmacokinetic studies
 - In vitro studies
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Microbiology:

Includes for anti infective drug products.

requires the following technical information and data:-

- A complete description of the biochemical basis of the drug action on microbial physiology
- The drugs antimicrobial spectrum
- Describe any known mechanism of resistance to the drug and provide information/data of any known epidemiologic studies demonstrating prevalence to resistance factor
- Clinical microbiology laboratory methods

Assure the sterility of the product through the manufacturing process – especially important with injectable drug products.

Safety data

- Statements in draft labeling
- Contra indications
- Warnings
- Precautions
- Adverse events

Statistical data

- All controlled clinical trial reports
- Integrated efficacy and safety summaries
- Integrated summary of risks and benefits
- **CASE REPORT TABULATION:-** Includes complete tabulation for each patient from every adequately well controlled phase II and Phase III efficacy, clinical pharmacology study. It also tabulation of safety data from all clinical studies.
- **CASE REPORT FORMS:-** Includes the complete CRF for each patient who died during a clinical study or adverse event, regardless of whether the AE is considered to be related to the study drug, even if the patient was receiving a placebo or comparative drug.

Inspections/Testing:

- Assure manufacturing facilities are in compliance with current good manufacturing practices (cGMPs)
 - Assure bioequivalence sites are in compliance with current good clinical practices (cGCPs)
 - Conducted primarily by Field/Office of Regulatory Affairs with support from Center (Office of Compliance) and assigned geographically
 - Labs are in the Office of Regulatory Affairs and the Center
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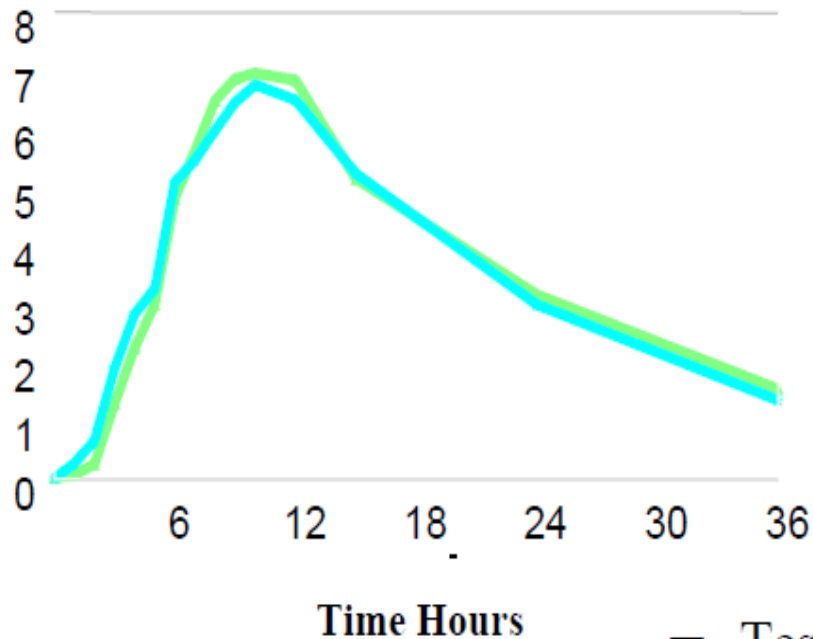
Bioequivalence:

A generic drug is considered to be bioequivalent to the brand name drug if:

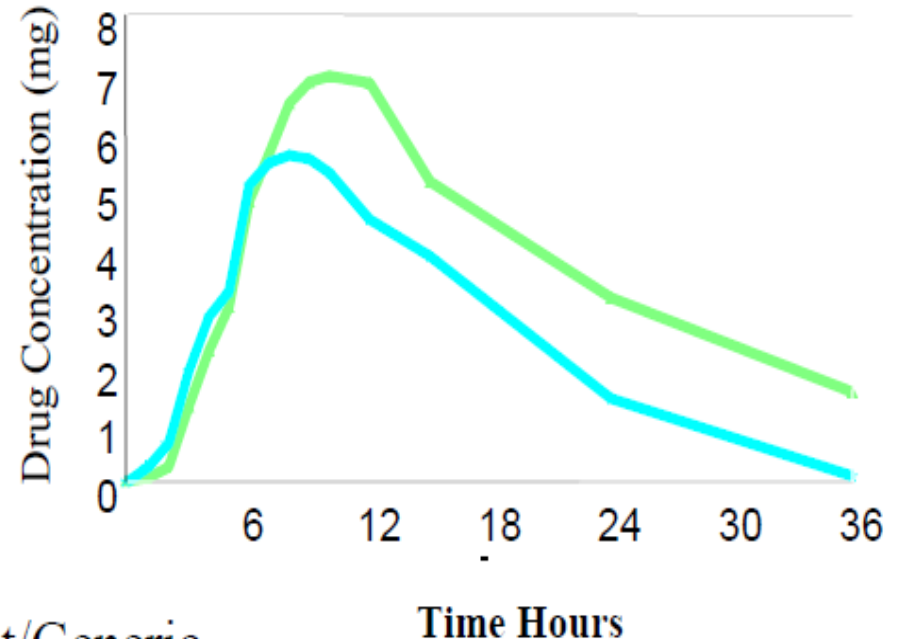
- *The rate and extent of absorption do not show a significant difference from listed drug, or*
 - *The extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant.*
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Bioequivalence – contd:

Bioequivalent

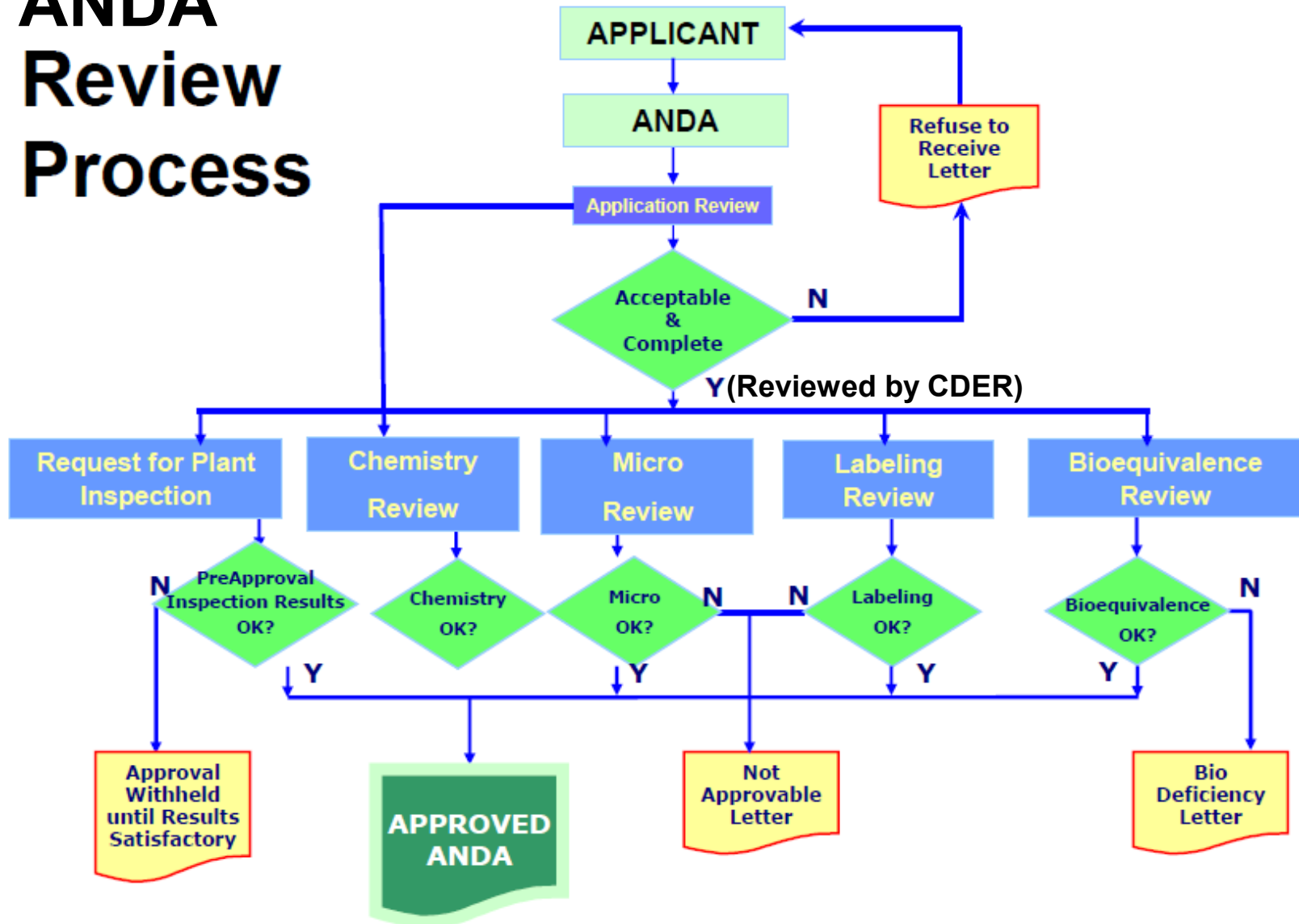


Inequivalent



■ Test/Generic
■ Reference/Brand

ANDA Review Process



Center for Drug Evaluation and Research – (CDER)

- The center reviews applications for new and generic pharmaceuticals, manages US cGMP regulations for pharmaceutical manufacturing, determines which medications require a medical prescription, monitors advertising of approved medications, and collects and analyzes safety data about pharmaceuticals that are already on the market.
- CDER reviews New drug Applications to ensure that the drugs are safe and effective. It is one of the Centers at the FDA. Its primary objective is to ensure that all prescription and over-the-counter(OTC) medications are safe and effective when used as directed.

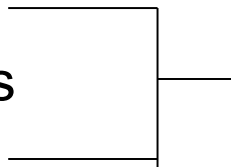
NDA vs. ANDA Review Process

(NDA) Requirements

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

(ANDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence



Conclusion:

NDA

Applicable for new drug
Take longer time (12-15 years)
More expenditure of money
Cost of drugs are more
Nonclinical studies and clinical investigations are essential

ANDA

Applicable for generic drug
Compare to NDA less time taken(1-2 years)
Comparatively less
Cost of drugs are less
Nonclinical studies and clinical investigations are nonessential except bioavailability and bioequivalence

TIME FRAMES FOR REVIEWING ANDA BY FDA:

- Within 180 days of receipt of an application for a new drug under section 505(b) of the act or an abbreviated application for a new drug under section 505(j) of the act,
- FDA will review it and send the applicant either an approval letter under 314.105 or a complete response letter under 314.110. This 180-day period is called the "initial review cycle."
- At any time before approval, an applicant may withdraw an application under 314.65 or an abbreviated application under 314.99 and later submit it again for consideration.
- The initial review cycle may be adjusted by mutual agreement between FDA and an applicant or as provided in 314.60 and 314.96, as the result of a major amendment.

Filing of ANDA:

- Within 60 days after FDA receives an application, the agency will determine whether the application may be filed.
 - The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.
 - If FDA finds that none of the reasons for refusing to file the application apply, the agency will file the application and notify the applicant in writing.
 - The date of filing will be the date 60 days after the date FDA received the application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the "filing clock."
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APPROVAL OF ANDA:

- FDA will approve an application and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling.
 - Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.
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AMENDMENTS TO AN UNAPPROVED ANDA:

- An applicant may amend an abbreviated new drug application that is submitted, but not yet approved, to revise existing information or provide additional information.
 - Submission of an amendment containing significant data or information before the end of the initial review cycle constitutes an agreement between FDA and the applicant to extend the initial review cycle only for the time necessary to review the significant data or information and for no more than 180 days.
 - The applicant shall submit a field copy of each amendment.
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Brand Name----Generic Name----Availability in 2011

Uroxatral-----	alfuzosin-----	July
Zyprexa-----	olanzapine-----	October
Lipitor-----	atorvastatin-----	November
Caduet-----	amlodipine-----	November
Tazorac-----	tazarotene cream-----	November

Brand Name----Generic Name----Availability in 2012

Lexapro-----	escitalopram-----	February
Entocort EC-----	budesonide-----	February
Avandia-----	rosiglitazone-----	March
Avandaryl-----	glimepiride-----	March
Avandamet-----	metformin-----	March
Boniva-----	ibandronate-----	March
Seroquel-----	quetiapine-----	March
Avapro-----	irbesartan-----	March
Avalide-----	hydrochlorothiazide-----	March
Provigil-----	modafinil-----	April
Plavix-----	clopidogrel-----	May
Viramune-----	nevirapine-----	May
Lescol-----	fluvastatin-----	June
Tricor-----	fenofibrate-----	July
Clarinx-----	desloratadine-----	July
Singulair-----	montelukast-----	August
Actos-----	pioglitazone-----	August

References:

- *<http://www.fda.gov/cder/guidance/index.htm>.*
- *Modern pharmaceuticals 4th edition by Banker and Rhodes.*
- *Burgers Medicinal Chemistry and drug discovery – Vol-II.*
- *A Text Book of Pharmaceutical medicine 5th Edition by John p.Griffin and John O’Grady.*
- *Comprehensive Medicinal chemistry by Hansch, Sammer, Taylor.*
- *The Theory and Practice of Industrial Pharmacy by Leon Lachman.*