

IND, NDA, ANDA, CONCEPT OF PARA I TO IV, EXCLUSIVITY:CONTENT, FORMAT & APPLICATION

NEW DRUG APPLICATION (N. D. A.)

Introduction:

The New Drug Application (NDA) is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing. The goals of the NDA are to provide enough information to permit FDA reviewers to establish the following:

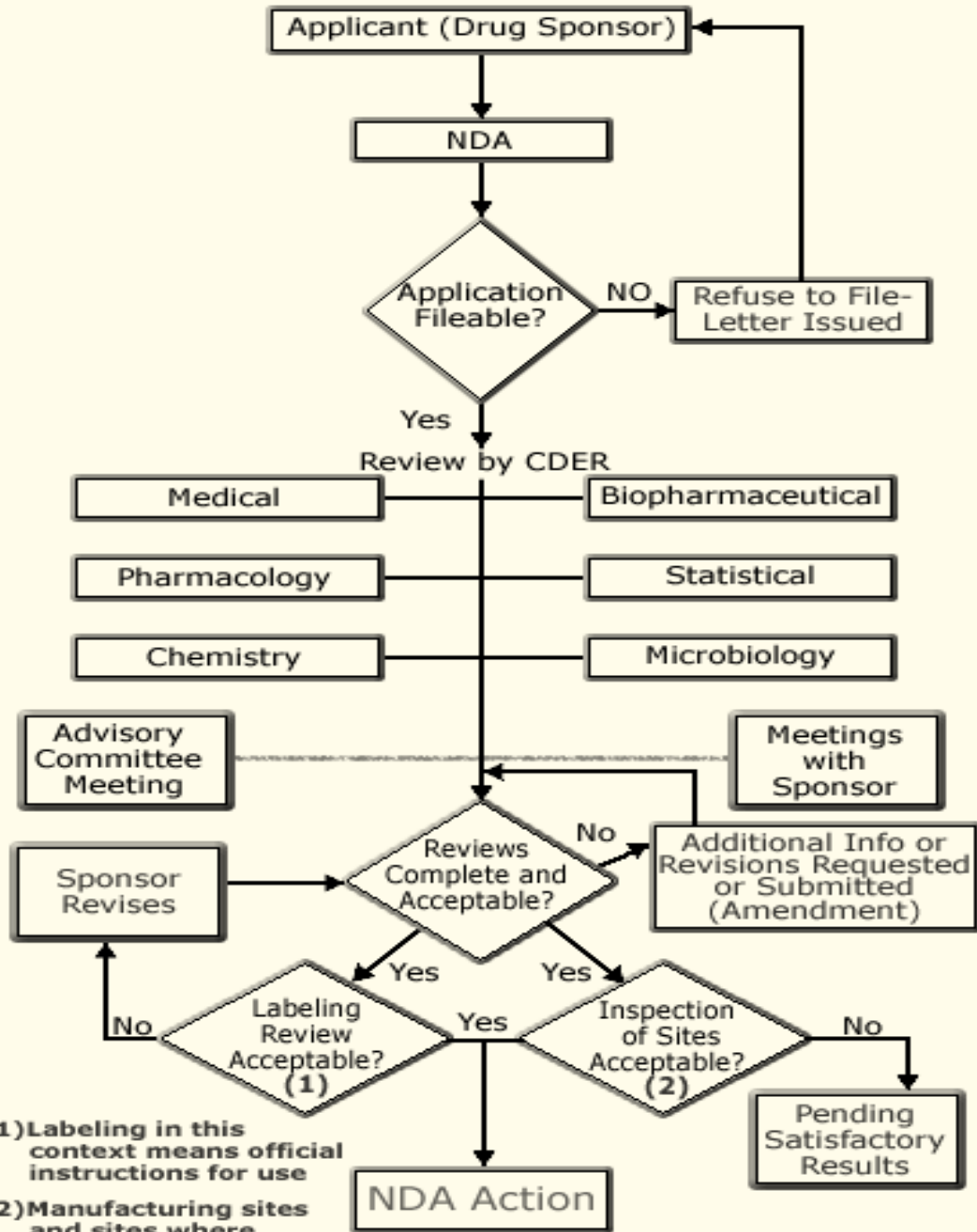
- Is the drug safe and effective in its proposed use(s) when used as directed, and do the benefits of the drug outweigh the risks?
- Is the drug's proposed labeling (package insert) appropriate, and what should it contain?
- Are the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug's quality adequate to preserve the drug's identity, strength, quality, and purity?

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) becomes part of the NDA.

- When the Food, Drug, and Cosmetic Act (FD&C Act) was passed in 1938, NDAs were only required to contain information pertaining to the investigational drug's safety. In 1962, the Kefauver-Harris Amendments to the FD&C Act required NDAs to contain evidence that a new drug was effective for its intended use as well, and that the established benefits of the drug outweighed its known risks.
- The NDA was again the subject of change in 1985, when the FDA completed a comprehensive revision of the regulations pertaining to NDAs. While this revision, commonly called the NDA Rewrite, modified content requirements, it was mainly intended to restructure the ways in which information and data are organized and presented in the NDA to easily access FDA reviews.

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged. The following resources provide summaries on NDA content, format, and classification, plus the NDA review process:

NDA Chart



1) Labeling in this context means official instructions for use

2) Manufacturing sites and sites where significant clinical trials are performed

Resources for NDA Submissions

The following resources have been gathered to provide the legal requirements of a new drug application, assistance from CDER to help meet those requirements, and internal NDA review principles, policies and procedures.

Guidance Documents for NDAs:

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications 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.

Guidance documents to help prepare NDAs include:

- 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.
- Container Closure Systems for Packaging Human Drugs and Biologics.
- Format and Content of the Chemistry, Manufacturing and Controls Section of an Application.
- Format and Content of the Microbiology Section of an Application.
- Format and Content of the Clinical and Statistical Sections of an Application.
- Format and Content of the Summary for New Drug and Antibiotic Applications.
- Formatting, Assembling and Submitting New Drug and Antibiotic Applications.
- Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
- Documentation for the Stability of Human Drugs and Biologics.
- Samples and Analytical Data for Methods Validation.
- Supporting Documentation in Drug Applications for the Manufacture of Drug Products.
- NDAs: Impurities in Drug Substances.
- Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application.
- Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application.
- Clinical Evidence of Effectiveness for Human Drug and Biological Products: Describes the quantity of evidence, and the documentation of the quality of evidence necessary to support a claim of drug effectiveness.
- 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.
- Qualifying for Pediatric Exclusivity. Certain applications may be able to obtain an additional six months of patent exclusivity.
- PET Drug Applications.
- Refusal to File. (Clarifies CDER's decisions to refuse to file an incomplete application).

Laws, Regulations, Policies and Procedures:

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act*²⁴ are the basic food and drug law of the U.S. With numerous amendments, it is the most extensive law of its kind in the world. 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 (CFR):

The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *CFR*. The *CFR* is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *Federal Food, Drug and Cosmetic Act* related statutes. Section 21 of the *CFR* contains :

all regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

- 21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

CDER's Manual of Policies and Procedures (MaPPs):

These documents are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well.

MaPPS of particular interest to NDA applicants include:

- 5015-6 Review of the Same Supplemental Change to More than One NDA or ANDA in More than One Review Division
- 6010.5 NDAs: Filing Review Issues 6020.8. Action Packages for NDAs and

Efficacy Supplements .

- 6050.1. Refusal to Accept Application for Filing From Applicants in Arrears
- 7211.1. Drug Application Approval 501(b) Policy
- 7600.6. Requesting and Accepting Non-Archivable Electronic Records for New Drug Applications.

Fundamentals of NDA Submission

As outlined in Form FDA-356h, Application to Market a New Drug for Human Use Or As An Antibiotic Drug For Human Use, NDAs can consist of as many as 15 different sections:

- Index
- Summary
- Chemistry, Manufacturing, and Control;
- Samples, Method Validation Package, and Labeling
- Nonclinical Pharmacology and Toxicology
- Human Pharmacokinetics and Bioavailability
- Microbiology (for anti-microbial drugs only);
- Clinical Data;
- Safety Update Report (typically submitted 120 days after the NDA's submission);
- Statistical;
- Case Report Tabulations;
- Case Report Forms;
- Patent Information;
- Patent Certification; and
- Other Information.

NDA Content and Format Requirements

- NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.
- The FDA has numerous guidelines that relate to NDA content and format issues. These guidelines can be obtained from CDER's Drug Information Branch (DIB).

Classification of drugs in NDA

- ❖ CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1 through 7 are used to describe the type of drug:
 - New Molecular Entity
 - New Salt of Previously Approved Drug (not a new molecular entity)
 - New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
 - New Combination of Two or More Drugs
 - Already Marketed Drug Product - Duplication (i.e., new manufacturer)

- New Indication (claim) for Already Marketed Drug (includes switching marketing status from prescription to OTC)
- Already Marketed Drug Product - No Previously Approved NDA

The following letter codes describe the review priority of the drug:

S - Standard review: For drugs similar to currently available drugs.

P - Priority review: For drugs that represent significant advances over existing treatments.

GENERAL REQUIREMENTS for filing an NDA

The new (present) NDA regulations require that an application be submitted in two copies :

- (A) an archival copy that serves as a permanent record of the submission, and
- (B) a review copy.

- The review copy is made up of a number of separate technical volumes, each tailored to the needs of the disciplines involved in the review.
- Both the archival and review copies are submitted in hard copy, the regulations permit an application to submit the archival copy as microfiche.
- The NDA application form (FORM NDA 356 h) consists of: Twelve items (including index) deals with the safety and efficacy features of drug product, two are concerned with patent information.

The archival copy is a complete copy of an application submission and must be bound in a **BLUE** cover jacket.

The archival copy should include a cover letter to:

- (i) confirm any agreements or understanding between the FDA and the applicant;
- (ii) Identify a contact person regarding the application;
- (iii) Identify the reviewing division of the FDA and include HFD number; and
- (iv) convey any other important information about the application.

The review copy is divided into six technical sections (“review sections”) and should be submitted with each review section separately bound in a specific color: (i) Chemistry, Manufacturing and Controls (CMC) – **RED**; (ii) Nonclinical Pharmacology and Toxicology – **YELLOW**; (iii) Human Pharmacokinetics and Bioavailability – **ORANGE**; (iv) Microbiology (if required) – **WHITE**; (v) Clinical Data – **LIGHT BROWN**; (vi) Statistical – **GREEN**.

Each review section should contain the following: (i) a copy of the cover letter attached to the archival copy; (ii) a completed application form FDA 356h; (iii) a copy of the summary (defined below); (iv) a copy of the general index of the entire application; (v) an index specific to that particular review section; (vi) letters of reference or authorization, if appropriate; and (vii) patent information.

Applicants may request supplies of the jackets (with appropriate color coding) from the FDA or an applicant may obtain jackets from commercial sources if it meets FDA specifications.

The Application (archival and review copy) must be bound on the left side of the page and use U.S. standard-size loose leaf page size (8.5” x. 11”). The pages must be hole

punched 8.5" centered and should be bound in the volume format with fasteners rather than three-ring binders.

Volumes submitted should be no more than two inches thick. The front cover of each volume should display the name of the applicant, the name of the drug, and the application number, if preassigned. The lower right hand corner of the jackets should be marked "___ of ___ volumes" with the correct number of volumes and specific volume, while the upper right hand corner of the jackets should be marked "Volume ___" with the correct specific volume.

The application form is supplemented with detailed, technical guidelines to improve the quality of submissions:

- The format and content of an application summary
- Formatting, assembling and submitting new drug and antibiotic applications
- The submission in microfiche of the archival copy of an application
- The format and content of the human Pharmacokinetics and Bioavailability section of an application
- The format and content of the clinical and statistical sections of an application.
- The chemistry section, because of its length, and highly detailed sections dealing with the manufacturing and control processes, is required to be submitted 90-120 days prior to the submission of the application for facilitating the identification of deficiencies in the filed NDA.
- Submission of chemistry section earlier than 120 days and less than 90 days before the remainder of the application will not be accepted.
- The archival copy of the application should include a comprehensive index by volume and page number. It is recommended that additional copies of the index be prepared and included with any material submitted to FDA for the NDA. This will easily access locating important parts of the submission that may be needed for meetings / view by individual technical reviewers.

SUMMARY

- It has been suggested that the summary consists of 50 - 200 pages. The summary should discuss all aspects of the application and needs to be written at approximately level of detail required for publication and meet the editorial standards applied by referred scientific and medical journals.
- It is advantageous to provide data in the summary in tabular and graphic form with clear explanation of any terminology used in the tabulations or graphics.

THE SAFETY UPDATE REPORTS

- The required safety data (from view point of clinical studies, animal studies, other sources generated or reported to sponsor) must be submitted in same format as integrated summary of safety described under clinical data section of the NDA content and format (21 CFR 314.50). Additionally the NDA format is required to include case report forms for each patient who died during a clinical study or who did not complete the study due to an adverse event.
- Safety update reports must be submitted :

- (a) Four months after the initial submission of an application,
- (b) Following receipt of an approvable letter and
- (c) Other times as requested by the FDA.

CHEMISTRY, MANUFACTURING AND CONTROLS

- Important point is the specific citation needed for the solid state forms of the drug substance and their relationship to bioavailability.
- Chemistry, manufacturing and controls summary must *provide a general overview of the drug substance and drug product.*
- Drug substance:
Description including physical and chemical characteristics and stability
- Drug product:
Composition and type of dosage form, manufacture, specifications and analytical methods, container/closure system, stability, investigational formulations.
- Details are provided in 21CFR 25.1

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

- Nonclinical laboratory studies include any in vivo/invitro experiment with the test drug to determine its safety, activity or disposition. This section includes Toxicological effects of drugs on reproduction and the developing fetus, ADME animal experiments of the drugs
- This section should provide a description, tabulation and graphics from Nonclinical laboratory studies of drug.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

- First section : There should be an overall tabulated summary of all in vivo biopharmaceutic studies carried out on the drug grouped by type of study.
- Second section : The summary of bioavailability or pharmacokinetic data and overall conclusions (C_{max}, t_{max}, K_{el}, AUC etc.)
- Third section : List of all formulations used in clinical trials and in vivo bioavailability or pharmacokinetic studies together with each formulation used in studies.
- Fourth section : Analytical methods used to measure the levels of drug and major metabolite
- Fifth section : Dissolution data on each strength and dosage form for which approval is being sought. A comparative dissolution study with the lot(s) used. In vivo biopharmaceutics studies should also be included.

MICROBIOLOGY

- Applicable to anti-infective and antiviral drugs.
- It should include description of :
 - Biochemical basis of the drug's action / microbial physiology.
 - Antimicrobial spectra of the drug, including results of invitro preclinical studies that demonstrate effectiveness.

- Any known mechanisms of resistance to the drug, including results of epidemiological studies to demonstrate prevalence of resistance factors.
- Clinical microbiological laboratory methods needed for effective use of the drug.

CLINICAL DATA

- This section includes descriptions, summaries and analysis of:
- Clinical pharmacology studies including animal study and toxicology.
- Controlled clinical studies including the protocol and description of the statistical analysis used to evaluate the studies.
- Uncontrolled clinical studies, including all necessary details of the studies.
- Any other data/information relevant to an evaluation of safety and effectiveness obtained from any source, foreign or domestic (U.S.).

STATISTICS

Statistics section should include:

- A statistical evaluation of the clinical data
- A copy of the data given in the description and analysis of each controlled clinical study, along with the statistical analysis.
- A copy of the data included in the integrated summary of all available information about the safety of the drug.

LABELING

A critical part of the NDA is the proposed labeling, which includes container labels, package insert, and any patient information leaflet. Actually, technical sections c, d, e, and f (above) are evaluated by the FDA to see if they support the indications and directions for use spelled out in the package insert. Sponsors often “push the envelope”—by wording the indications for the drug as widely as possible, and by downplaying the importance of the drug’s side effects—in their proposed labeling, and negotiations to finalize the labeling often occur when the NDA has been reviewed and deemed “approvable” by the Agency.

Case Report forms and tabulations

The sponsor must submit data tabulations from each Phase II and Phase III study and also the case study report form for every clinical trial patient who died or withdrew from the study because of an adverse event.

Patent Information

Information must be submitted regarding any patent held by the sponsor that covers the drug substance, formulation, and composition of the drug product, or method of use. Upon approval of the NDA, this information is published in the FDA’s Orange Book (known formally as Approved Drug Products with Therapeutic Equivalence Evaluations) and serves as a guide to firms wishing to develop generic copies of the innovator’s product.

Drug Samples

Samples of the new drug substance and drug dosage form are not submitted with the NDA, but are submitted upon the FDA's request to the District Laboratory assigned to test them.

NDA REGULATIONS

Review Time Frames (21 CFR 314.100):

This time frames includes:

- Within 180 days of receipt of an application, the FDA will review and issue an approval, approvable, or not approvable letter. This 180-day period is called the 'review-clock'
- During the review period an applicant may withdraw an application (21 CFR 314-65) and later resubmit it.
- The time period may be extended by mutual agreement between the FDA and the applicant or as the result of submission of a major amendment (21 CFR 314.60)

Filing Time Frames (21 CFR 314.101):

- Within 60 days after the FDA receives an application, a determination will be made whether the application may be filed.
- This will determine whether sufficient information is provided to proceed with an in-depth review of application.
- If FDA files the application, the applicant will be notified in written. The date of filing will be the date 60 days after the FDA received the application.
- The date of filing begins the 180-days period of the review. If FDA refuses to file the application, the sponsor will be given the opportunity to meet with FDA to discuss the reasons why the application is not file able.

APPROVAL OF NDAs BASED SOLELY ON FOREIGN DATA (21 CFR 314.106)

Clinical data will be considered on merit regardless of country of origin. Foreign Clinical data meeting U.S. criteria for approval may be approved if:

- The foreign data are applicable to the U.S. Population and U.S. Medical practice.
- The studies have been performed by clinical investigators of recognized competence.
- If an inspection is necessary, FDA is able to validate the data through an on-site inspection or other appropriate means or the data may be considered valid without the need for an on-site inspection by FDA.
- FDA will apply this policy according to the nature of the drug and the data being considered. The FDA is willing to explore all areas to remove the need to conduct repetitive clinical testing in U.S. When adequate foreign data have been generated a pre-NDA submission meeting is encouraged when approval being solely on foreign data is sought.

FDA DIALOGUE ON SCIENTIFIC & MEDICAL ISSUES (21 CFR 314.102)

- Approximately 90 days after the NDA is received, the FDA will provide applicants with an opportunity to meet with reviewers to discuss the general progress and status of the application
- Particularly for new chemical entities and major new indications of marketed drugs, this meeting will generally be held at the applicant's option and may be held by telephone.
- With the issuance of an approvable/not approvable letter, an opportunity will be provided to applicants to meet with the FDA and discuss what further steps need to be taken before the applications can be approved. Priority for these meetings will be given to applications for new chemical entities and major new indications for marketed drugs.

NDA PRE-APPROVAL AND POST- APPROVAL SAFETY REPORTS

In 21 CFR 314.50 (d) (5) (vi) (b), the FDA details the necessity to periodically update a pending application with new safety information which affects the statements of contraindications, warnings, precautions and adverse reactions in the draft labeling. The safety update reports are required to include the same kinds of information from clinical or animal studies as well as other sources, and must be submitted in the same format as the previously described integrated summary of safety.

These safety reports must be submitted as follows:

- Four months after the initial submission
- Following receipt of an approvable letter
- At other times as requested by FDA

In case of any adverse drug experience, the surveillance system requires the reporting of such experience as soon as possible within 15 working days of initial receipt of the information. These 'alert reports' are required to be submitted on Form FDA 1639 (Drug Experience Report). All reactions subject to 15 day alert report require follow-up reports within 15 working days of receipt of new information

Even if no such reports are reported, the follow up reports has to be submitted in separate cover and as a summary / tabular form to be presented in periodic report

- NDA holders must review periodically (quarterly for the first three years and yearly thereafter) the frequency of adverse drug experience reports that are serious and unexpected and report any significant increase in frequency (e.g. a doubling) within 15 working days to determine whether a significant increase in frequency exists or not.
- Applicants must adhere to a reporting schedule that calls for submission of each quarterly and each annual report within 60 days of the anniversary date of approval of the application.
- A 15-day alert report based on information from the scientific literature must be accompanied by a copy of the published article. These literature reports should be either case reports or the reporting of a formal clinical trial
- Applicants should not include in post-marketing adverse experience reports of any adverse experiences that occurred in clinical trials if they were previously submitted as part of the approved application.

NDA REVIEW TIMES

Following deficiencies are typically encountered in drug development:

- Sponsors do not pursue advice from the FDA regarding their drug development plan
- Sponsors routinely move ahead to the next clinical trial without completely analyzing results of the most recent trial
- Sponsors sometimes provide a minimal amount of data in an effort to get drug approvals

COMPUTER ASSISTED NEW DRUG APPLICATION (CANDA)

- Concept: it is designed to shorten FDA review time by submitting data to FDA in a form ready for manipulation by a computer.
- Importance is given on the clinical sections of the NDA, as they require the maximum time to review and often require manipulation of the data by FDA.
- In a September 15, 1988 Federal Register Notice, FDA stated to increase the use of computers in field of improving efficiency of the drug review process. FDA had not provided exact blue print on how to best organize / submit a CANDA, but two basic computer systems have been developed so far:
 - Involves keeping the data on a mainframe computer that is operated either by the sponsor / by the computer company assisting it with FDA able to access the information via a telephone connection.
 - Putting the data on a floppy disk, laser disc, etc. for use by FDA via desktop computers that are provided by the sponsor.
- One possible concern of CANDAs is the possibility of 'data dredging' by FDA reviewers, that is pursuing tangential rather than Central issues because the computer makes it easy to do so, but this has not been observed routinely.

HOW TO IMPROVE NDA HANDLING

- ❖ Be sure to supply additional (desk copy) submissions of the clinical data section and integrated summaries of safety and efficacy for the medical reviewer; the pharmacokinetic and bioavailability summary for the biopharmaceutics reviewer; the chemistry, manufacturing, and control process summary for the statistician reviewer; and extra copies of draft labeling for the medical reviewer.
- ❖ The submission should be placed in a proper jacket binders: use the proper numbering system
 - If requested, be prepared to submit for review draft copies for advertising and promotional material to be used in the initial or launch campaign to the Division of Drug Advertising and Labeling (HFN-240).
 - Place the IND, NDA, or petition number on every letter or submission: include supplement numbers where applicable.

- ❖ Submit new information in reviewable bundles or marketed with references suitable to all the material FDA reviewers need to consider in making a decision – this will help avoid lengthy file searches.
- ❖ FDA files are chronological: submissions stating “this replaces, corrects, or updates section or page so-and-so,” do not fit well in the FDA document-tracking or review system.

REGULATIONS APPLICABLE TO NDA

It is noteworthy to be familiar with the regulations applicable to the NDA. The general NDA requirements are coded in Title 21, Code of Federal Regulations, Part 314.

- Subpart A contains the general provisions, section 314.1 to 314.3
- Subpart B details the sections for applications as follows:
 - a. Application
 - b. Index
 - c. Summary
 - d. Technical Sections: Chemistry, manufacturing and controls, Non-clinical pharmacology and toxicology, Human pharmacokinetics and bioavailability, Microbiology, Clinical data, Statistical
 - e. Samples and labeling
 - f. Case report forms and tabulations
 - g. Other
 - h. Format of an original application

Current New Drug Application Requirements

Understanding the requirements behind the FDA’s New Drug Application process can save substantial time in the development of biopharmaceuticals and allow companies in the life sciences sector to appropriately plan strategies that will maximize efficiency, control costs, and engage in clinical trials that provide real data on safety and efficacy while moving the product into the market much faster.

Upon discovery of a product and proof-of-concept, a company should begin thinking about what it requires to advance the product into clinical trials or to seek permission to begin marketing, where no trials are required by regulation. Preclinical testing and data lay the foundation for obtaining permission to commence human trials and therefore become an integral part of the FDA regulatory filings.

The approval process, where required, differs for each type of product. For example, approval of a pharmaceutical is different than approval of a device, which is different from approval of a dietary supplement. Understanding the approval process of a given product can be instructive in designing and implementing the development process.

Biopharmaceuticals are subject to rigorous preclinical and clinical testing and other approval requirements by the FDA under the U.S. Food, Drug, and Cosmetic Act and by

comparable agencies in most foreign countries. Various federal, state, and foreign statutes govern or influence the manufacture, labeling, storage, record-keeping, and marketing of such products. Pharmaceutical manufacturing facilities may also be subject to regulation by state, local, and other authorities.

IND Application

The FDA imposes substantial requirements and conditions on therapeutic drug products, including lengthy and detailed laboratory and clinical testing procedures, sampling activities, and other costly and time-consuming processes. After preclinical testing, as required by the applicable regulations, an Investigational New Drug (IND) application must be filed with the FDA to obtain authorization for human testing through clinical trials.

This application includes a description of the overall plan for investigating the drug product and a comprehensive protocol for planned studies.

Pursuant to the regulations, the FDA usually asks companies to submit a description of the drug substance, including its physical, chemical, and biological characteristics, as well as a description of the general method of preparation of the drug substance and a list of all components, including inactive ingredients.

A section of the IND describes the composition, manufacture, and control of the drug substance. The drug company must provide sufficient information to assure the proper identification, quality, purity, and strength of the investigational drug.

The IND should also contain adequate information about pharmacological and toxicological studies of the drug, involving laboratory animals and other tests on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical trials. Where there has been widespread use of the drug outside of the U.S., it is possible in some limited circumstances to submit a well-documented clinical experience as part of the required preclinical work.

Once the FDA approves the IND, the sponsor is allowed to enter the clinic where certain reporting requirements, such as making progress reports on the study or studies covered by the IND, must be met and the sponsor must alert the FDA and clinical investigators immediately of any unforeseen serious side effects or injuries.

NDA Submission

When clinical testing has been completed and analyzed, final manufacturing processes and procedures are in place, and the company has ready other required information, it must submit a New Drug Application (NDA) to the FDA. No action can be taken to market any therapeutic drug product in the U.S. until the FDA has approved an NDA.

The data in the NDA must establish that the drug is safe for use under the proposed labeling conditions and is effective for its proposed use(s). Substantial evidence is defined by statute and FDA regulation to mean evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts qualified by scientific training and experience, to evaluate the effectiveness of the drug involved.

The NDA must contain data-obtained outlines from the clinical trials of the drug, as well as a description and analysis of the drug's pharmacokinetics. It must also include a description and analysis of any other data relevant to the safety and effectiveness of the drug product obtained from any source, foreign or domestic.

The NDA also includes an integrated summary of all available information about the safety of the drug product, including potential adverse effects and clinically significant potential adverse reactions with other related drugs.

A section of the NDA discusses the statistical, controlled clinical study and the documentation and supporting statistical analysis used in evaluating the controlled clinical studies. Another section describes bioavailability of the drug, including the data concerning the action of a drug in the human body over a period of time and the extent of drug absorption in the human body or information supporting a waiver of the submission of such data.

The NDA must describe the composition, manufacture, and specification of the drug substance, including a full description of the drug substance, its physical and chemical characteristics, and its stability; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance, as well as the availability of the drug products made from the substance.

NDA's contain lists of all components used in the manufacture of the drug product and a statement of the specifications and analytical methods for each component.

INVESTIGATIONAL NEW DRUG APPLICATION (I.N.D.A.)

Definition:

The investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials).

General introduction:

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

Types of INDs:

Investigator INDs: An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Commercial INDs: They are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. However, there is another class of filings broadly known as "noncommercial" INDs.

The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs."

Emergency Use IND: This IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR Sec.312.23 or Sec.312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

Treatment IND: Other name is Expanded Access IND, this IND may be submitted for experimental drugs showing promise in clinical testing of serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place (21 CFR 312.34).

The present format of IND was designed as IND Rewrite which is effective from June 17, 1987.

The main objectives of the IND Rewrite are as follows:

- To focus FDA's attention during early phase of clinical research on assuring the safety of human test subjects
- To provide sponsors with a greater measure of flexibility in conducting Phase 1 trials.
- To facilitate consultation between FDA & sponsors, especially after there is an indication that the new drug is safe and efficacious in humans.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- *Animal Pharmacology and Toxicology Studies* - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- *Manufacturing Information* - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- *Clinical Protocols and Investigator Information* - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

An IND must also include an *Investigator's Brochure* which is a document intended to educate the trial investigators of the significant facts about the trial drug they need to know to conduct their clinical trial with the least hazard to the subjects or patients who will be enrolled.

EXEMPTIONS:

Clinical studies conducted with marketed drugs are exempted from IND regulations provided that the investigations are conducted in compliance with the institutional review (21 CFR 56) & informed consent (21 CFR 50) requirements and the regulation prohibiting the promotion or sale of investigational drugs

Investigations with marketed drugs that are intended to support new indications or significant changes in labeling or advertising do not qualify for the exemption.

Any kind of study involving changes in route of administration, dosage level or other factors which would significantly increase the risks associated with the use of the product would not qualify for the exemptions.

WAIVERS:

Clinical studies conductance can be waived by FDA if an acceptable justification is provided by sponsor. FDA may grant the request for a waiver if it deems that the sponsor's noncompliance would not pose a significant or unreasonable risk to human test subjects.

A waiver request is required to contain at least one of the following:

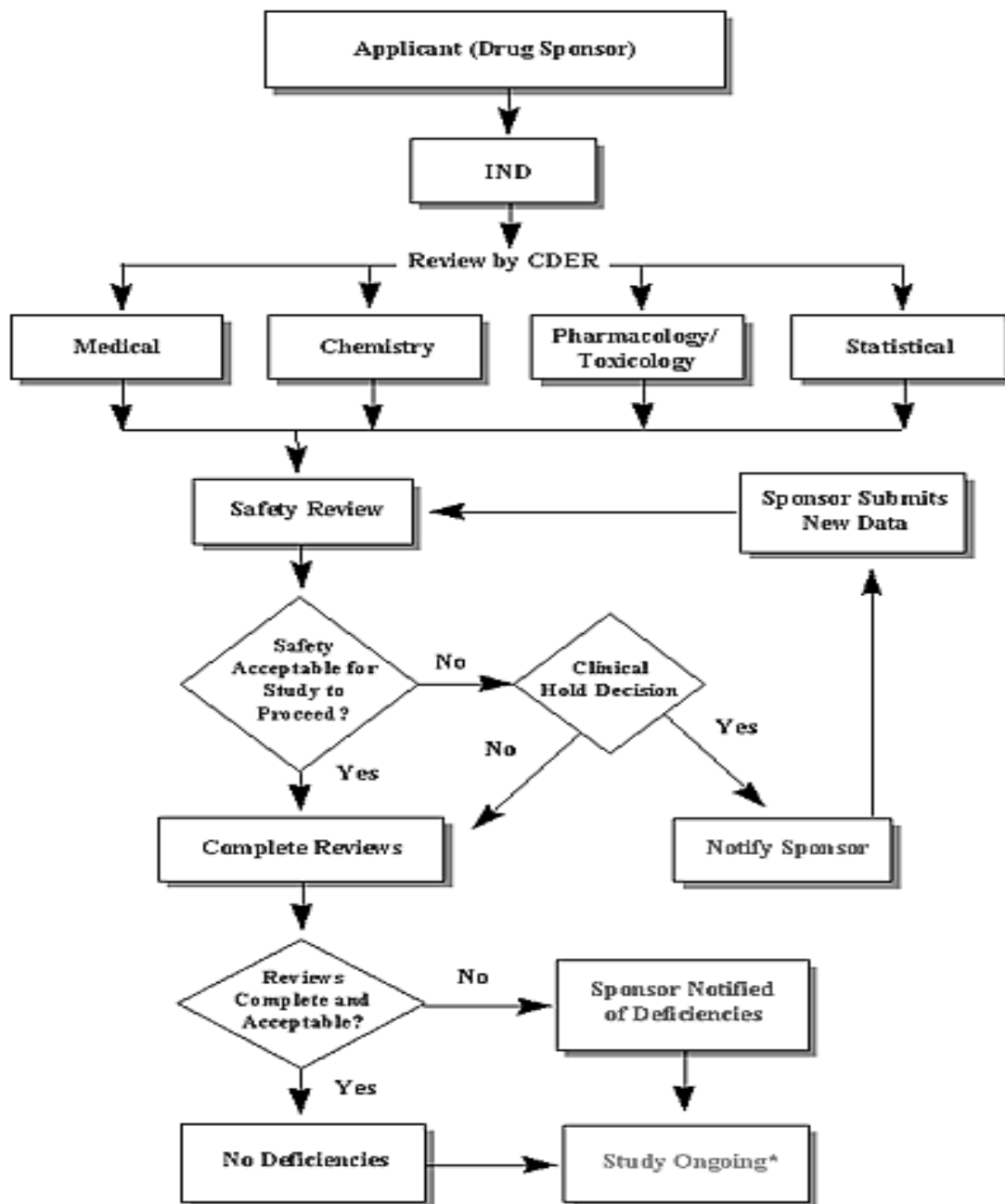
- (1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

- (2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

- (3) Other information justifying a waiver.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

IND Chart



* While sponsor answers any deficiencies

Criteria for application:

A clinical study is required for an IND if it is intended to support a:

- New indication
- Change in the approved route of administration or dosage level
- Change in the approved patient population (e.g. pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
- Significant change in the promotion of an approved drug

Application submission:

Most INDs are paper submissions. While only 12% of INDs are submitted electronically, 28% of IND Amendments are submitted electronically a result of maintaining a growing number of INDs submitted electronically to date.^[1]

Additional regulations:

- Experimental drugs under an IND must be labeled, "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

Noteworthy examples:

The FDA closed its medical marijuana IND program (the Compassionate Investigational New Drug program) in 1991, facing an influx of AIDS patients seeking access to the drug. Seven patients continue to receive cannabis from the government under the program

Resources for IND Applications

The following resources have been gathered to provide the legal requirements of an IND application, assistance from CDER to help meet those requirements, and internal IND review principles, policies and procedures.

Pre-IND Consultation Program: CDER offers a Pre-Investigational New Drug Application (IND) Consultation Program to foster early communications between sponsors and new drug review divisions in order to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated [Pre-IND Consultation List](#).

Guidance Documents for INDs:

Guidance documents to help prepare INDs include:

- Guidance for Industry: CGMP's for Phase 1 Investigational Drugs
- Guidance for Industry: Exploratory IND Studies
- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well Characterized, Therapeutic, Biotechnology-Derived Products.
- Q & A - Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. This guidance is intended to clarify when sponsors should submit final, quality-assured toxicology reports and/or update the Agency on any changes in findings since submission of non-quality-assured reports or reports based on non-quality-assured data.
- 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.
- IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer.
- Drug Master Files: 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.
- Immunotoxicology Evaluation of Investigational New Drugs. This guidance makes recommendations to sponsors of investigational new drugs (INDs) on (1) the parameters that should be routinely assessed in toxicology studies to determine effects of a drug on immune function

(2) When additional immunotoxicity studies should be conducted, and

(3) When additional mechanistic information could help characterize the significance of a given drug's effect on the immune system.

Laws, Regulations, Policies and Procedures

Code of Federal Regulations (CFR): The following regulations apply to the IND application process:

21CFR Part 312	<u>Investigational New Drug Application</u> ²²
21CFR Part 314	<u>INDA and NDA Applications for FDA Approval to Market a New Drug</u> ²³ (New Drug Approval)
21CFR Part 316	<u>Orphan Drugs</u> ²⁴
21CFR Part 58	<u>Good Lab Practice for Nonclinical Laboratory [Animal] Studies</u> ²⁵
21CFR Part 50	<u>Protection of Human Subjects</u> ²⁶

21CFR Part 56	<u>Institutional Review Boards</u> ²⁷
21CFR Part 201	<u>Drug Labeling</u> ²⁸
21CFR Part 54	<u>Financial Disclosure by Clinical Investigators</u> ²⁹

Requirement for an IND:

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

Phases of an investigation:

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are as follows:

(a) Phase 1: (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) Phase 2: Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c)Phase 3: Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

FORMAT & CONTENT OF AN IND

Following sections are contained in an IND:

1. Cover Sheet (Form FDA 1571)
2. Table of Contents
3. Introductory Statement & General investigational plan
4. Investigator's Brochure
5. Protocols
6. Chemistry, Manufacturing & Control Information
7. Previous Human Experience with the Investigational Drug
8. Additional Information

1. Cover Sheet (form FDA 1571):

The form is provided for basic information like name of drug, submission date, sponsor identification, phase of proposed clinical investigation, sponsor commitments, identification of clinical monitor and safety evaluator, information regarding transfer of responsibilities to a contract research organization.

2. Table of Contents:

Item	Title	Volume/ page
Drug Name® IND table of contents		
3	Introductory statement & General Investigational Plan...	
	(i) Introductory Statement...	
	(ii) Summary of Previous Human Experience with the Drug...	
	(iii) If the Drug Has Been Withdrawn from Investigation / Marketing...	
	(iv) General Investigational Plan...	
5	Investigator's Brochure...	
6	Protocol...	
7	Chemistry, Manufacturing & Control Information...	
	(a) Drug substance.....	
	(b) Drug Product.....	

	(c) Placebo (if applicable)...
	(d) Labeling.....
	(e) Environmental Analysis...
8	Pharmacology & Toxicology Information...
9	Previous Human Experience with the Investigational Drug.....
	(i) Summary of Previous Human Experience...
	(ii) If the Drug is a Combination of Drug Previously Investigated / Marketed.....
	(iii) If the Drug Has been Marketed Outside the United States... ..
10	Additional Information (as applicable for radioactive drugs or drugs with dependence or abuse potential).....

The sections of the IND are numbered in accordance with 21 CFR 312.23, specifying IND format and content.

3. Introductory Statement & General Investigational Plan:

It consists of four subsections:

	1st subsection (introductory statement)	2nd subsection	3rd subsection	4th subsection
C O N T E N T S	<ul style="list-style-type: none"> Name of drug P'cological Class Structural formula Route of administration Broad objectives Planned duration of the proposed clinical investigation 	Brief summary of any previous human experience with the drug, including investigational or marketing experience in other countries	It is a statement as to whether or not the drug has been withdrawn from investigation or marketing in any country for any reason of safety or efficacy	Brief description of overall investigational plan for drug during the following year like: Indications to be studied, kinds of clinical trials to be conducted in first

4. Investigator's Brochure:

Definition:

It is a body of information characterizing the drug product that is given by a sponsor to each participating clinical investigation.

The Investigator's Brochure is a constantly evolving document that grows as the knowledge gained from research with the investigational drug grows. While a drug is under an accepted IND, application, the Brochure serves as the approved labeling for the substance. As such, it must contain summaries of each and every study conducted with the investigational drug, and often contains text on similar drugs of the same class, if such information is useful and/or necessary for an investigator.

Importance of Investigator's Brochure:

- It provides the clinical investigator with all the known information and research on the drug under study
- It serves as the approved labeling for the investigational drug; and,
- It contains the basic summaries of all research done to date on the investigational drug for filing the IND/NDA.

Investigator's Brochure has to be honest, accurate, up-to-date, and complete, as well as clear, concise, and easy-to-read.

Drug Name® Investingator's Brochure Table of contents	
<u>Page</u>	
Introduction.....	
Chemistry.....	
Physical Properties.....	
How Supplied.....	
Pharmacology.....	
Specific Effect Studies...	
General Studies.....	
Toxicology.....	
Acute Toxicity.....	
Multidose Toxicity.....	
Special Toxicity Studies...	
Reproductive Studies.....	
Mutagenicity Studies.....	
Pharmacokinetics.....	
Preclinical.....	
Clinical.....	
Clinical Trial.....	
Phase 1.....	
Phase 2/3... ..	
Safety/Efficacy Overview	
Safety.....	
Efficacy.....	
Possible Risks and Side Effects...	
References.....	

5. Protocols:

- Phase 1 protocols are may be less detailed and more flexible than those for Phase 2 or Phase 3.

- Phase 1 protocol provides an outline of investigation by specifying information as estimated number of test subjects, inclusion/exclusion criteria and dosing plan
- It is specific in safety and monitoring of vital sign and clinical laboratory evaluations.
- Phase 2 and Phase 3 protocols are detailed, describing all aspects of the studies, such that any deviation in a design if required, it can be established in the protocol from the beginning.

All protocols are required to contain the following elements:

- Statement of the objectives and purpose of the study
- Patient inclusion/exclusion criteria
- Estimate of number of patients to be studied
- Description of study design
- Dosing information including planned maximum dosage and duration of individual patient exposure to the Drug
- Description of the observations and measurements planned to fulfill the study objectives
- Description of the clinical procedures, laboratory tests, or other methods employed to monitor the effects of the drug in the subjects and to minimize risk
- Statement of commitment to obtain IRB approval before initiating the clinical investigation
- Form FDA 1572 which provides for such critical information as name and address and a statement of qualifications of each investigator, name of each sub investigator, name and address of the research facilities to be used and the name and address of each reviewing IRB (international regulatory board)

6. Chemistry, Manufacturing & Control Information:

- **Drug Substance:**

Information regarding the physical, chemical or biological characteristics of the drug substance, along with the name and address of the manufacturer.

Description of the general method of preparation, identification of the analytical methods and acceptable limits used to assure the identity, purity and strength of the drug substance.

Stability data must be sufficient to support the stability of drug substance throughout the preclinical and proposed clinical studies.

- **Drug Product:**

Qualitative & Quantitative compositions are required; information regarding the manufacturing facility, manufacturing and packaging procedure description, identification of analytical methods, acceptable limits used to assure identity, purity, and strength of components and finished products. Stability data to support duration of proposed clinical studies.

Same information may be submitted for placebo where applicable.

- **Labeling:**

A copy of all labels and labeling to be provided to each clinical investigations must be submitted

- **Environmental Analysis:**

Unless, if IND falls as per 21 CFR 25.24 defined exclusion, an environmental analysis must be submitted this includes: identification and quantities of any chemical substances emitted during the manufacture of the product, use of resources and energy, mitigation measures etc.

Pharmacology & Toxicology Information:

Summary of the Pharmacology & Drug disposition, integrated toxicological summary, toxicological data tabulation.

7. Previous Human Experiences with the Investigational Drug:

Such findings if available must be submitted whether drug is marketed in U.S. or other foreign country.

8. Pharmacology and toxicology information:

Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.

(i) Pharmacology and drug disposition: A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) Toxicology: An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity

9. Additional Information: In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) Drug dependence and abuse potential: If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) Radioactive drugs: If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) Pediatric studies: Plans for assessing pediatric safety and effectiveness.

(iv) Other information: A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

- **IND Safety Reports:**

If a sponsor notify any unexpected fatal / life threatening experience associated with the use of the drug requires to notify the FDA by telephone no later than 3 working days after receipt of the information, followed by a written report within 10 days.

- **IND Annual Reports:**

Annual report comprising the annual progress made by sponsor to FDA with in 60 days of the effective date of the IND which includes following seven sections:

1. individual study information	<ul style="list-style-type: none"> ● Brief summary of status of each study in progress and each study completed during previous year. ● E.g. title of study, patient population, initially planned no. of patients, actual entered into study, no. of them dropped out of study due to any reason
2. summary information	<ul style="list-style-type: none"> ● Most freq. & serious adverse experiences by body system ● Tabulation of all safety reports ● Preclinical work in progress & completed ● Summary of significant manufacturing / microbiological changes made during past year
3. Updated Investigational Plan	Focusing the plan for forthcoming year
4. Updated Investigator's Brochure	Any updation made in Brochure
5. Phase I Modification	Any modification not reported in previous year
6. Foreign Marketing Development	Approval, Market withdrawn etc., in foreign
7. Outstanding Business (optional)	List of all issues of IND waited for FDA approval (this section is optional)

- **Withdrawal of an IND:**

- ✓ At any time a sponsor may withdraw an effective IND without prejudice.
- ✓ If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with 312.59.
- ✓ If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

- **Requirements for use of an IND in a Clinical Study & Clinical Holds:**

- IND will be placed in clinical study legally only when investigations of IND are to be conducted in compliance with the regulations governing institutional review boards (21 CFR 56) and informed consents (21 CFR 50)

- An IND goes into effect 30 days after the FDA receives it, unless FDA notify sponsor that application has been put on clinical hold
- If the FDA concludes that a deficiency exists in an IND, but it will not pose an immediate and serious risk to subjects, FDA will resolve the matter with sponsor before issuing a clinical hold order
- Resumption of the affected investigations will be authorized by the FDA when the sponsor has satisfactorily corrected the deficiency.
- **Inactive Status:**
 - On sponsor's request FDA may place an IND on inactive status if no subjects have entered clinical studies for atleast two years or if the IND has been on clinical hold for atleast one year
 - After remaining on inactive status for five years, the FDA may terminate an IND.

Emergency use of an investigational new drug (IND):

- Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with 312.23 or 312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means.

Conclusion:

Two important outcomes from the IND discussion:

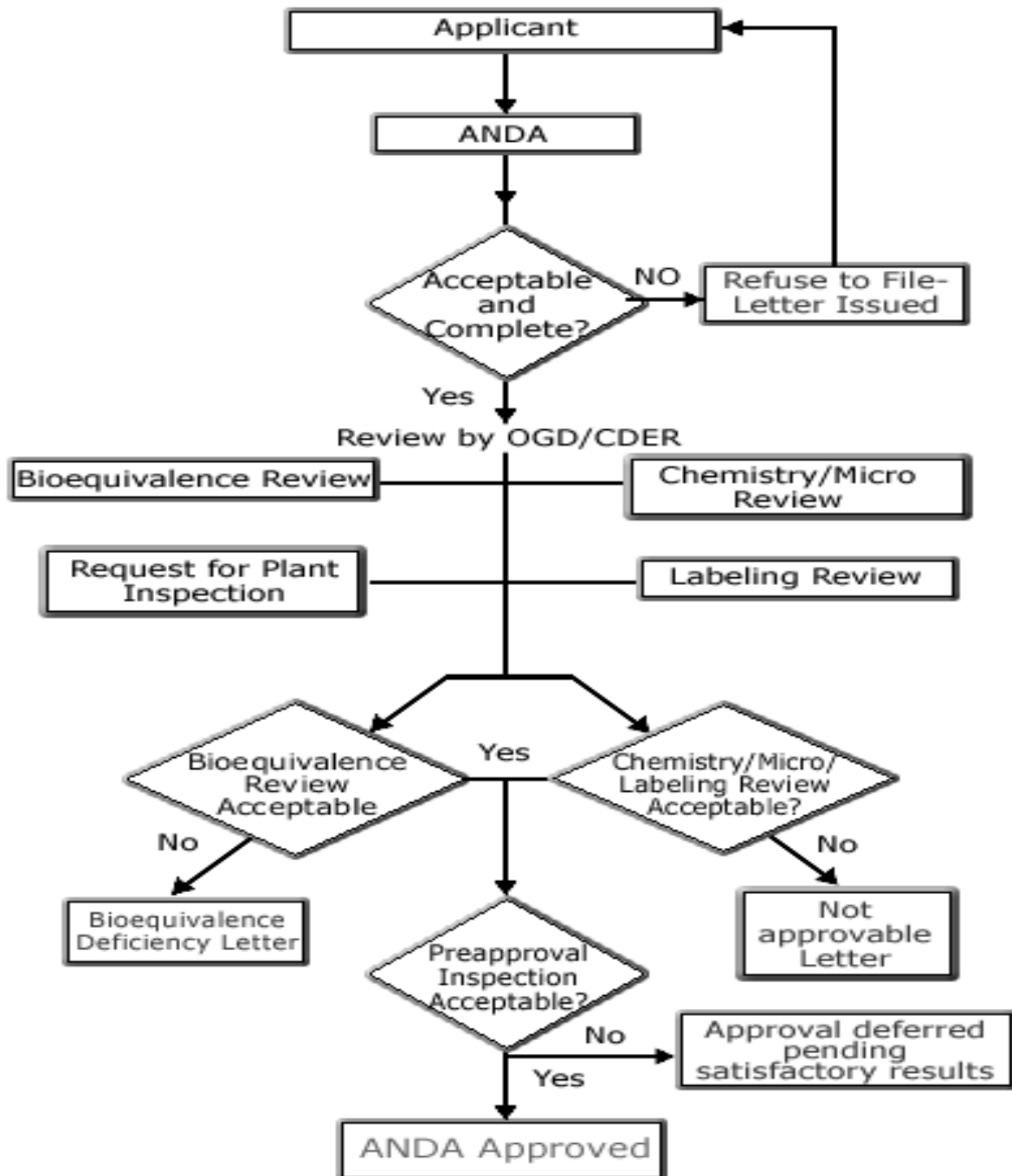
- ❖ 30 days after an IND is submitted to the FDA, if the sponsor has not heard anything from the FDA it can be assumed that the drug is not on a clinical hold and clinical trials may be started
- ❖ The Investigator's Brochure, which will be used during that important first clinical study and in every clinical study thereafter, acts as the approved labeling for the drug while it is under an IND

ABBREVIATED NEW DRUG APPLICATION (A.N.D.A)

INTRODUCTION:

- An Abbreviated New Drug Application (ANDA) contains data submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, for review and ultimate approval of a generic drug product.
- Once ANDA is approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the public.
- A generic drug product is the one that is comparable to an innovator drug product in **dosage form, strength, route of administration, quality, performance characteristics and intended use**. 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 bioequivalent (i.e., performs in the same manner as the innovator drug). One of the ways that scientists use to demonstrate bioequivalence is to measure the time taken by the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This will give them the rate of absorption or bioavailability of the generic drug, which they can then compare to that of the innovator drug. **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.**
- Use of bioequivalence as the base for approving generic drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the WAXMAN-HATCH ACT. 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. At the same time, the brand-name companies (innovators) can apply for up to 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.
- Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.

Generic Drug (ANDA) Review Process



Resources for ANDA Submissions

The following resources have been gathered to provide the legal requirements of an ANDA application, assistance from CDER to help meet those requirements, and internal ANDA review principles, policies and procedures.

Guidance Documents for ANDAs

The FDA has numerous guidances that relate to ANDA content and format issues. Below is a list of some recent Guidances of interest.

Guidance documents to help prepare ANDAs are listed together in the following categories:

- Generics :
 - Generics (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 postapproval 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.
- 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.

Laws, Regulations, Policies and Procedures

Code of Federal Regulations (CFR): ***The following regulations apply to the ANDA process:***

- 21CFR Part 314 Applications for FDA Approval to Market a New Drug or and Antibiotic Drug.
- 21CFR Part 320 Bioavailability and Bioequivalence Requirements.
- 21CFR Part 310 New Drugs.

GUIDELINES AVAILABLE FOR ANDA:

- Various guidelines have been developed to assist applicants in preparing and filing ANDAs. These guidelines describe:
 - Format & content for the following sections:
 - a. Application summary
 - b. Chemistry, Manufacturing and controls section

- c. Non clinical pharmacology and toxicology section
- d. Human pharmacokinetics & bioavailability section
- e. Clinical and statically section
- f. Microbiology section

➤ Various guidelines available for ANDA includes:

1. Organization of ANDA
2. Electronic submission of data for ANDA
3. Submission of archival copy of application in Microfiche
4. Guideline for impurities in drug substances
5. Guideline for submitting supporting documentation for the Manufacture of Drug substance.
6. Guideline for submitting supporting documentation for the Manufacture of finished dosage forms.
7. Guideline for submitting supporting documentation for stability studies of Human drugs and Biologics.
8. Guideline for packaging
9. Guidelines for changes in approved ANDA and NDA
10. 180 days exclusivity under Hatch Waxman amendment
11. Guidelines for alternate source of API in pending ANDAs
12. Post marketing reporting of Adverse Drug reactions

FILING OF ANDA:

- In order to file ANDA all required items should be in proper order (organization). Detail information is available under Regulation 21 CFR 314.50, 21 CFR 314.94 and 21 CFR 314.440
- Office of Generic Drug (OGD) strongly encourages submission of the bioequivalence, chemistry and labeling portions of an application in electronic format.

DIFFERENCE BETWEEN SUBMISSION OF NDA AND ANDA:

- A New Drug Application (NDA) requires the submission of :
 1. Well-controlled clinical studies to demonstrate effectiveness
 2. Preclinical and clinical data to show safety
 3. Detailed descriptions of manufacturing and packaging procedures
 4. Proposed **annotated** labeling referencing all studies from which statements contained in the package insert has been derived.
- In contrast to NDA, ANDA requires the submission of :
 1. Detailed descriptions of the components
 2. Manufacturing, controls, packaging, and labeling (which can be in final, printed form), data sufficient to assure the bioavailability or bioequivalence of the drug to be marketed. The labeling should be prepared in accordance with that specified in DESI (**Drug efficacy study implementation**) Notice or other Federal Register

Notice. The manufacturing and controls information to be provided are the same as required for a New Drug Application

BIOAVAILABILITY AND BIOEQUIVALENCE :

Subpart A cover general provision while subpart B contain 18 sections delineating the following general BA or BE.

1. Requirement for the submission of BA and BE data.
2. Criteria for the waiver of an in vivo BA, BE data.
3. Basis for demonstrating in vivo BA or BE.
4. Type of evidence to establish BA or BE.
5. Guideline for conduct of in vivo BA studies.
6. Guideline on design of single dose BA studies.
7. Guideline on design of multiple dose in vivo BA studies.
8. Correlation of BA with an acute pharmacological effect or clinical evidence.
9. Analytical method for an in vivo BA study.
10. Inquiries regarding BA and BE requirement and review of protocol by FDA.
11. Applicability of requirement regarding an IND application.
12. Procedure for establishing and amending a BE requirement.
13. requirement for batch testing and certification by FDA
14. Requirement for in vitro batch testing of each batch.
15. Requirement for maintenance of records of BE testing.
16. Retention of BA sample.
17. Retention of BE sample

MANUFACTURING AND CONTROL REQUIREMENTS OF THE ANDA:

- One of the most critical portions of an ANDA is, Item 3 of the form FDA 356h, manufacturing and controls section.
- From 1977-1992, 105 Non approval letter issued by FDA due to chemistry & manufacturing deficiencies. an

FDA Manufacturing and Controls guidelines:-

1. Guideline for the format and content of an application summary.
2. Guideline for the format and content of the chemistry, manufacturing, and controls section of an application.
3. Guideline for stability studies for Human drugs and Biologics
4. Guideline for packaging of Human Drugs and Biologics.
5. Guideline for submitting supporting documentations in drug applications for the manufacture of drug substances.
6. Guideline for submitting supporting documentation for the manufacture of finished dosage forms.
7. Guidelines for drug master files.

- According to this guidelines information that applicant provide should prove that the proposed product is the same as listed product with respect to its indications for use, active ingredients(s), route of administration, dosage form, strength, bioavailability, and labeling.

- Requirements for Drug substances sources:

- The drug substances used in manufacturing of products are frequently obtained from one or more manufactures, frequently locate overseas. So, it is important to obtain a copy of potential supplier's most recent establishment inspection report describing FDA's findings. This document should be reviewed by the applicant to check acceptability of that manufacturer by FDA.
- In addition, the supplier should have a DMF available at FDA for reference purposes .This will describes the facilities, personnel, equipment, and manufacturing & controls procedure used at the site (s) where the bulk drug substance is made.

Specifications for drug substances:-

- Sometimes assay methodology is not specified into the monograph for older drugs or method described is not specific. In such cases FOI request to FDA for a copy of pertinent regulatory assay method. This will be helpful in minimizing the amount of analytical development work to be carried out.
- Carefully evaluate impurity peaks observed in a supplier's bulk substance and compare them with those observed in the marketed product.
- The extent that the peaks differ may **determine the need to obtain further information**, including toxicity.
- If samples of impurities, degradation products are available from the supplier or are identified in published literature then the assay methods should be appropriately validated by the ANDA sponsor for their sensitivities and specifications with respect to them.
- It is also recommended that the sponsor of an ANDA set up and maintain a stability program for the bulk drug substance.

Drug product requirements:-

- Similar to NDA.
- The extent of stability data submitted, however, is much less than that usually available for an NDA.
- It is possible that the stability indicating Analytical method in the monograph is not appropriate or not present in monograph to and FOI to obtain a copy of regulations assay method.
- Adequate validation studies should be carried out to verify the accuracy, precision, specificity, recovery and sensitivity of the method(s) conducted by the

sponsor's product with those obtained with the original brand name product using the same methodology.

For example, data comparing the dissolution characteristics and performance of the sponsor's and the brand name tablet or capsule products at several different time points (as applicable to obtain 95% or more of drug in solution) otherwise referred to as comparative dissolution profiling- should be obtained

ANDA Expiration dates:-

- The FDA will tentatively approve a two year expiration date for a product if satisfactory data reflecting at least three months storage under accelerated conditions is submitted.
- The sponsor is also expected to provide a commitment to continue to monitor the stability of the product periodically report the results to FDA, and to remove from market any batches failing to meet specifications prior to product's labeled expiration period.
- Final approval for the expiration date is obtained when acceptable shelf life data for two years on more than one production lot is made available to FDA.

180-DAY GENERIC DRUG UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

INTRODUCTION:

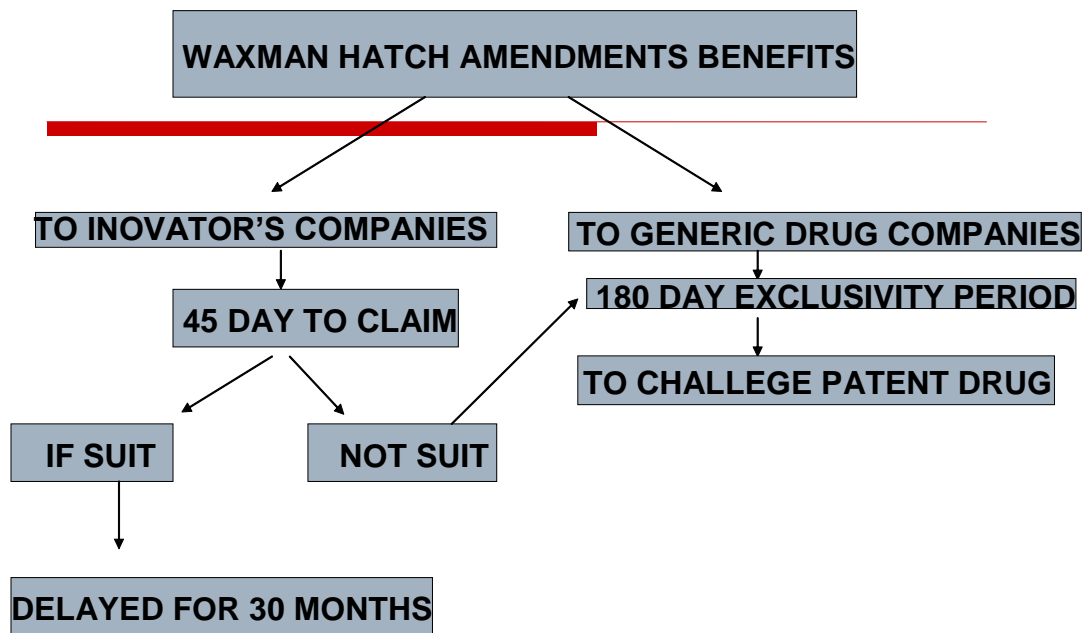
- Before Hatch Waxman amendment generic manufacturers can file ANDA only after innovators patent expiration or after cancellation of such patent. But under the section 505(j)(5)(B)(iv)² of Hatch Waxman amendment, Congress rewarded the first generic company to challenge the innovator company's patent for a given drug with a 180 day exclusivity period in which no subsequent abbreviated new drug application (ANDA) could be approved for that drug.

HATCH WAXMAN AMENDMENTS:-

It permit the preparation and the filling of the ANDA before patent expiration, it generally contemplated that the effective approval date of the generic would be on the expiration date of the patent covering the innovator original drug .the act however also establish another procedure as a generic company could challenge a patent and try to enter the market before patent expiration.

- This amendment added a patent notification system to U.S. law. As a result, generic companies can readily find and file the patent(s) that cover the innovator's drug.

- This Amendment tells that the innovator should be notified of the generics intent to challenge the patent. Thus it helps innovator to take timely legal action.
- Both the generic companies and the innovator companies are provided with certain benefits by virtue of the ANDA notification system. For the generic companies, the Hatch-Waxman amendments provide an incentive a 180- day exclusivity period in which no other ANDA for that drug can be approved. This 180-Day period is to encourage generic companies to challenge the validity of orange book listed patents or to design around these patents to bring more quickly a generic drug to market and also to recoup the possible costs. Whereas for the innovator company filing of an ANDA for a product that is intended to be marketed before expiration of the orange book patent is an act of patent infringement. So if the innovator drug company brings suit within 45 days, the approval of the generic company's ANDA is delayed for upto 30 months or until a court rules otherwise.



- Under this amendment polymorphs and novel products are patentable, provided bioequivalent. However novel processes of old product are not patentable.

CONCEPT OF PARAGRAPH I TO IV:

- For filing ANDA, generic company must include a patent certification as per section 505(j) (2) (A) (vii) of the Hatch Waxman Act. This certification has to make one of the following statements:

- I. No patent information on the drug product that is the subject of the ANDA has been submitted to FDA
 - II. That such patent has expired
 - III. The date on which such patent expires
 - IV. That such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product which the ANDA is submitted.
- The first three paragraphs (I, II, III) results in no generic drug being sold during the term of the innovator's patent protection.
 - In case paragraph IV certification generic drugs can be sold during the term of the innovator's patent protection. However to overrule this paragraph certification, if innovator brings suit within 45 days for patent infringement then the generic company's ANDA cannot be approved for 30 months unless :
 - a. The court decides that such patent is invalid or not infringed. In this case ANDA approval is made effective on the date of the court decision
 - b. The court decides that such patent has been infringed and sets a date for approval of the ANDA as provided.
 - c. The court grants a preliminary injunction prohibiting the ANDA applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement.

SUBSTANTIALLY COMPLETE ANDA:

- Under the proposed rule, only the applicant submitting the first "Substantially complete ANDA" with a paragraph IV certification with respect to patent in the Orange book for the listed drug would be eligible for exclusivity.
- To be "Substantially complete" it is proposed that the application must contain all of the information required like bioequivalence, etc.
- If a new bioequivalence study is required to obtain approval of the ANDA then the application would be considered not substantially complete and the applicant would not be eligible for exclusivity.
- Another way to lose exclusivity is to withdraw paragraph IV certification either voluntarily or as a result of a settlement or defeat in patent litigation by first applicant. Now in such case if first applicant again submit paragraph IV certificate and there are no subsequent applicants for 180 days exclusivity then first applicant would be eligible for exclusivity.
- If there is other applicant that has submitted a paragraph IV certification for the same drug product neither the first applicant nor the any subsequent applicant would be eligible 180 day exclusivity.
- The FDA has provided an exception in its proposed rule with respect to loss of exclusivity due to an ANDA being not substantially complete.

HOUSE KEEPING REGULATIONS:

- If the first applicant is sued and loses the patent litigation under 21CFR314.107© (4) then such applicant would be required to change its certification from paragraph IV to a paragraph III. As a result he will lose claim for exclusivity.
- The FDA Proposed that all ANDA applications containing Paragraph IV certifications for a particular drug product that are received by the FDA on the same day will be eligible for exclusivity if no other ANDA with a paragraph IV certification for the drug product had been filed on an earlier day. All such same day applicants would be considered first applicants.

PATENT EXPIRATION REGULATION

- If the patent for which the first applicant filed a paragraph IV certification expires, then the first applicant is no longer eligible for exclusivity and the FDA may approve all other wise eligible ANDAs.

TRIGGER PERIOD

- Sometime there is unnecessary delay in entry of generic drug into the market. This can happen because of delay in approval of ANDA by FDA or because of some kind of settlement between first generic (first ANDA approver) and innovator. As for example say first generic who has got 180 day exclusivity rights tells to innovator that it will not start its 180 days until x number of days in return to Y number of dollars from innovator. Thus as per rule until first generic finishes 180 day exclusivity period no other generic manufacturer can be granted 180 exclusivity period. As a result innovator and first generic enjoys undue advantage. To counter this FDA has involved new concept called “Triggering period”
- Under this concept the commencement of the 180-day exclusivity period for the first applicant is either the first commercial marketing of the first applicant’s product, or a decision of a court holding the patent invalid, not infringed, or unenforceable, whichever is earlier.
- The FDA also proposes setting a time for the exercise of exclusivity, specifically a 180-day ‘triggering period’ during which there must either be a court decision regarding the patent favorable to the first applicant or the first applicant must begin commercial marketing of its product. If neither of these events occurs in the triggering period then the first generic would lose its eligibility for exclusivity and subsequent generic filers for ANDA would be eligible for immediate approval.
- There is new ‘triggering period’ which is separate and distinct from the 180-day ‘exclusivity period.’ The triggering period would begin upon the :
 - a. Tentative approval of a subsequent ANDA with a paragraph iv certification for the same drug product
 - b. Expiration of a 30 month stay of ANDA approval due to patent litigation
 - c. Expiration of a preliminary injunction prohibiting marketing of an ANDA product

- d. Expiration of the statutorily described exclusivity periods for the listed drug
- The FDA has also proposed shortening the length of the triggering period to 60 days if a first applicant has already received final approval at the time of the tentative approval of subsequent ANDA, and either has not been sued as a result of its patent certification, or has been sued and the case was settled or dismissed without a decision on the merits of the patent claim.
- The FDA has also proposed that if the first applicant is sued as a result of its paragraph IV certification and the patent litigation is ongoing, then the triggering period would not begin at least until the 30 month period has lapsed. At the end of the 30 month period, the triggering period would begin on the date a subsequent applicant receives tentative approval, or if a subsequent applicant had previously received tentative approval then on the date the 30 month period expired. During the 180- day triggering period, the first applicant would have to begin marketing its product, or obtain a final court decision, to obtain its exclusivity.

WAIVER OF EXCLUSIVITY

- The current regulations do not address whether a first applicant can waive its 180 day exclusivity period to permit approval of a subsequent applicant. However the first applicant that has obtained 180 days of exclusivity by commercial marketing or a court decision of non-infringement, invalidity or unenforceability can waive exclusivity in favor of one or more subsequent applicants but not a specific applicant.

505(b) (2) APPLICATION:

- Section 505 of the FD&C Act describes 3 types of new drug application (NDA):
 1. An application that contains full reports of investigations of safety and effectiveness (Section 505 (b)(1))
 2. An application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (Section 505(b)(2))
 3. An application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (Section 505(j))

505(b)(2) Of the federal food drug and cosmetic act allow sponsor to obtain approval of new drug application based upon full report of investigation establishing a drug safety and efficacy. where such investigation were not conducted by or for the 505(b)(2) applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigation were conducted. Thus a 505(b)(2) application permits a sponsor to rely on the FDA finding of safety and efficacy for a previously approved drug product without requiring the sponsor to obtain a right of reference from the original applicant. The 505(b) (2) sponsor must

provide any additional clinical data necessary to demonstrate the safety and effectiveness of different between the original drug and the 505(b) (2) drug so while unnecessary duplication of preclinical and certain human and applicability of prior finding for your particular product formulation. section 505(b)(2) continuous to allow reliance on third party data that is available in published literature and which establish the safety and effectiveness of the drug.

BENEFITS:

Two important commercial benefits are available to 505(b)(2) sponsors including one that distinguish the 505(b)(2) route of approval from the abbreviated NDA and its method of petition to request a change from a listed drug.

1. A 505(b)(2) applicant may qualify for 3 or 5 year of hatch Waxman exclusivity as appropriate . This comparison to 180 days of exclusivity granted to the first ANDA applicant to challenge a listed product. However for 505(b) (2) applicant who does nor meet the requirement of either 3 or 5 year hatch Waxman exclusivity there is no 180 days exclusivity period available for being the first 505(b)(2) NDA to challenge the listed product.
2. an approved 505(b)(2) product such as approved ANDA product may received an AB substitutability rating in the orange book . thus for a therapeutic substitution perspective and under state formulatory law the 505(b)(2) applicant is not disadvantage relative to the generic ANDA drug.

SUPPLEMENTAL NEW DRUG APPLICATIONS

- Once an ANDA as an NDA has been approved, any significant changes in the conditions described in the application must first be approved via a supplemental NDA/ANDA.
- Any substantive modifications proposed for the formulation may require the submission of additional data assuring the bioavailability of the drug.
- Certain minor changes, however, as permitted by specific regulations, may be made without the filing of supplemental applications.
- Supplemental application I is filed for any changes occurring in chemistry, manufacture of drug, use, labeling, safety, effectiveness, identity, strength, quality or purity of the drug or the adequacy of the manufacturing methods, facilitation, and controls to preserve these elements.

Supplements to new drug applications requiring FDA approval before the change is made for the drug substance.

- a) Relaxation of specification limits
- b) The establishment of new regulatory limits
- c) The deletion of a specification or analytical method.
- d) A revision in the method of synthesis, including the use of different solvents or alterations in the approved route.
- e) The use of different facility or establishment for the drug substances manufacture, where the process used to produce the drug substance differs

materially from that approved in the NDA/ANDA and/or the facility has not received a current satisfactory, good manufacturing practice inspection within the last two years covering the manufacturing process.

Supplements to new drug applications requiring FDA approval before the change is made for the drug product.

- a) The addition or deletion of an ingredient or alteration of the composition (except for deletion of colorant.)
- b) The relaxation of specification limits.
- c) The establishment of a new regulations analytical method.
- d) A revision in the method of manufacture, including changing or relaxing and in process control.
- e) The use of a different facility or establishment, including a different of contract, laboratory, on labels, to manufacture, process, test, or pack the drug.
- f) The use of new container/closure system or a revision of a relevant specification (s) and regulatory analytical method(s).
- g) A change in container size (except for solid forms)
- h) An extension of the expiration date based on data obtained using a new or an unapproved revised stability testing protocol.
- i) The establishment of a new processing procedure for batches failing to meet quality assurance specifications.
- j) All labeling changes except for those specifically exempted.

Supplements for changes that may be made before FDA approval

- Changes in an ANDA that may be made before FDA approval most include a full explanation of the basis for the changes. It should identify the data on which the change will be made and in the case of labeling modification, contain 12 copies of final printed labeling.
 - The cover letter and the supplement should be plainly marked, "Special supplement changes being effected."
- a) The addition of a new specification (s) or test method.
 - b) Revisions in methods, facilities (Except for a new facility or controls to provide increase assurance of product, identity, quality, purity, and strength).
 - c) Revisions in labeling to add or strengthen:
 - i. A contraindication, warning, precaution or adverse reaction.
 - ii. An instruction about dosage and administration to further assure the safe use of the product.
 - iii. A statement about drug abuse, dependence, or over dosage.
 - iv. Revisions in labeling to delete false, misleading, or unsupported indications of use or claims for effectiveness.

Use of a different facilities or establishment to manufacture the drug substance, where the method of manufacture does not differ materially form that in the former facility and the new facility has received a satisfactory cGMP inspection within the last two year.

Procedures for submission of a supplement to an approved application :

- (a) Only the applicant may submit a supplement to an application.
- (b) All procedures and actions that apply to an application under 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

Change in ownership of an application:

- (a) An applicant may transfer ownership of its application. At the time of transfer the new and former owners are required to submit information to the Food and Drug Administration as follows:
 - (1) The former owner shall submit a letter or other document that states that all rights to the application have been transferred to the new owner.
 - (2) The new owner shall submit an application form signed by the new owner and a letter or other document containing the following:
 - (i) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application;
 - (ii) The date that the change in ownership is effective; and
 - (iii) Either a statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under 314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in 20.45 of FDA's public information regulations.
- (b) The new owner shall advise FDA about any change in the conditions in the approved application under 314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

Patent infringement can also occur by submitting an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA):

The most familiar type of patent infringement is that which arises from the manufacture, use, sale, or offer for sale of a product falling within the scope of a patent. Patent

infringement can also occur however by the simple act of submitting an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA). A lawsuit that was recently resolved on appeal demonstrates how this can happen.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Waxman-Hatch Act) contained provisions that amended both the Food and Drugs statute and the patent statute, and the effect of these provisions is seen when an ANDA is filed for a new formulation of a known drug.

The FDA provisions require an ANDA applicant to list all patents that claim the drug in some form and to certify that the new formulation raises no infringement liability under any of those patents. The applicant must also notify the owner of each listed patent and explain why the new formulation is believed to not infringe the patent.

The patent provisions state that if someone submits an ANDA with the intention of manufacturing, selling or using a drug while a patent is in force that covers the manufacture, sale or use, the submission of the ANDA will itself constitute infringement.

Thus, under the FDA statute, the patent owner is notified that a competitor intends to market the drug and is told why the competitor believes it can do so without infringing the patent, while under the patent statute the patent owner can sue the competitor immediately if the patent owner disagrees with the competitor's reasons for noninfringement.

This is exactly what happened with a new drug formulation developed by Mylan Pharmaceuticals Inc. The drug is glyburide, which is known to be effective in reducing the level of glucose in serum and is useful for treating Type II diabetes. The effectiveness of the drug is limited, however, by its low bioavailability (rate of entry into the bloodstream), and various solutions have been proposed. One of these is to prepare the drug in micronized form, i.e., as micronized particles compressed into a tablet, since micronized particles have a high surface area which helps them dissolve faster. Tableted drugs contain large amounts of excipients (inert substances that form a vehicle for the active ingredients), however, and particle size of both the drug and the excipients must be carefully controlled so that the tablet will have a uniform consistency and a uniform drug loading.

The excipient used with glyburide is lactose. Unfortunately, the formation of lactose particles with sufficient size control for use with micronized glyburide has been a cumbersome and costly process involving wet granulation, drying, and sizing or milling. A cheaper way was the subject of U.S. Patent No. 4,916,163, owned by Pharmacia & Upjohn Company, which was based on the discovery that lactose particles with a high degree of size control can be obtained directly by spray-drying. The patent therefore claims a micronized glyburide composition with "spray-dried lactose as the preponderant excipient."

The lactose in Mylan's glyburide formulation was not spray-dried but instead anhydrous, thereby differing both in its method of preparation and in its absence of the water of hydration present in spray-dried lactose. When Mylan submitted its ANDA, it listed the Pharmacia & Upjohn patent, notified Pharmacia & Upjohn, and explained that the

formulation would not infringe the patent since the formulation did not contain spray-dried lactose. Pharmacia & Upjohn did not dispute the distinction but claimed that the two forms of lactose were equivalent and that the Mylan formulation infringed under the "doctrine of equivalents." (Chemical Engineering Progress, Nov. 1997, p. 26).

Patent law states that the doctrine of equivalents will not be applied if applying it would be contrary to positions taken by the inventor or the inventor's attorney while the patent application was pending. Before the '163 patent issued, it had been rejected over earlier patents on lactose-containing glyburide formulations. In response to that rejection, Pharmacia & Upjohn stated that the lactose in the earlier patents was not spray-dried, and that spray-dried lactose was a critical feature of the invention and provided test data showing the manufacturing advantages of the spray-dried form. This was sufficiently convincing that the patent was granted.

The argument and the test data, however, prevented Pharmacia & Upjohn from later extending the scope of the patent to any form of lactose other than spray-dried. The question of whether anhydrous lactose and spray-dried lactose were equivalents in the suit against Mylan was, therefore, never reached, and the patent was deemed un infringed.

Suspension of approval of an abbreviated new drug application:

The approval of an abbreviated new drug application approved under 314.105(d) shall be suspended for the period stated when:

(1) The Secretary of the Department of Health and Human Services, under the imminent hazard authority of section 505(e) of the act or the authority of this paragraph, suspends approval of a listed drug referred to in the abbreviated new drug application, for the period of the suspension;

(2) The agency concludes that the risk of continued marketing and use of the drug is inappropriate, pending completion of proceedings to withdraw or suspend approval under 314.151 or

(3) The agency issues a final decision stating the determination that the abbreviated application is suspended because the listed drug on which the approval of the abbreviated new drug application depends has been withdrawn from sale for reasons of safety or effectiveness or has been suspended. The suspension will take effect on the date stated in the decision and will remain in effect until the agency determines that the marketing of the drug has resumed or that the withdrawal is not for safety or effectiveness reasons.

Procedures for suspension of abbreviated new drug applications:

When a listed drug is voluntarily withdrawn for safety or effectiveness reasons:

(1) If a listed drug is voluntarily withdrawn from sale, and the agency determines that the withdrawal from sale was for reasons of safety or effectiveness, the agency will send each holder of an approved abbreviated new drug application that is subject to suspension as a result of this determination a copy of the agency's initial decision setting forth the reasons for the determination. The initial decision will also be placed on file with the Division of Dockets Management (HFA305), Food and Drug Administration.

(2) Each abbreviated new drug application holder will have 30 days from the issuance of the initial decision to present, in writing, comments and information bearing on the initial decision. If no comments or information is received, the initial decision will become final at the expiration of 30 days.

(3) Comments and information received within 30 days of the issuance of the initial decision will be considered by the agency and responded to in a final decision.

(4) The agency may, in its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions.

(5) If the final decision affirms the agency's initial decision that the listed drug was withdrawn for reasons of safety or effectiveness, the decision will be published in the Federal Register in compliance with 314.152, and will suspend approval of all abbreviated new drug applications identified and remove from the list the listed drug and any drug whose approval was suspended. The notice will satisfy the requirement of 314.162(b).

The agency's final decision and copies of materials on which it relies will also be filed with the Division of Dockets Management.

(6) If the agency determines in its final decision that the listed drug was withdrawn for reasons of safety or effectiveness but, based upon information submitted by the holder of an abbreviated new drug application, also determines that the reasons for the withdrawal of the listed drug are not relevant to the safety and effectiveness of the drug subject to such abbreviated new drug application, the final decision will state that the approval of such abbreviated new drug application is not suspended.

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